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(54) **Imidazoles for the treatment of atherosclerosis.**

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EP-A- 0 236 628
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Description

Field of the Invention

This invention relates to imidazoles as inhibitors of acyl-CoA: cholesterol acyltransferase (ACAT), processes for their preparation, and their use as antihypercholesterolemic agents.

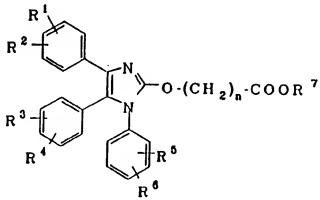
US-A-4 137 234 describes in Examples 21, 22 and 53 certain N-methyl-N'-[(3-(2-imidazolylthio)propyl]-urea compounds which are disclaimed herein.

Background of the Invention

Hypercholesterolemia is an established risk factor in the development of atherosclerosis. Therapeutic agents which control the level of serum cholesterol have proven to be effective in the treatment of coronary artery disease. While agents exist that can modulate circulating levels of cholesterol carrying lipoproteins, these agents have little or no effect on the intestinal absorption of cholesterol. Dietary cholesterol can increase the level of serum cholesterol to levels which place an individual at increased risk for the development or exacerbation of atherosclerosis. Since much of the free or unesterified cholesterol that is absorbed by intestinal mucosal cells must first be esterified by ACAT prior to its incorporation and secretion into the bloodstream in large lipoprotein particles called chylomicrons, inhibition of ACAT can reduce the absorption of dietary cholesterol. In addition, the accumulation and storage of cholesteryl esters in the arterial wall is associated with increased activity of ACAT. Inhibition of the enzyme is expected to inhibit the formation or progression of atherosclerotic lesions in mammals.

There are a limited number of patents in the literature disclosing compounds which are useful as ACAT inhibitors in particular and antiatherosclerotic agents in general. For example, U.S. Patent No. 4,623,662, issued to De Vries on November 18, 1986, discloses ureas and thioureas as ACAT inhibitors useful for reducing the cholesterol ester content of an arterial wall, inhibiting atherosclerotic lesion development, and/or treatment of mammalian hyperlipidemia. U.S. Patent No. 4,722,927, issued to Holmes on February 2, 1988, discloses disubstituted pyrimidineamides of oleic and linoleic acids as ACAT inhibitors useful for inhibiting intestinal absorption of cholesterol.

U.S. Patent No, 4,460,598, issued to Lautenschläger et al. on July 17, 1984, discloses compounds of the formula:

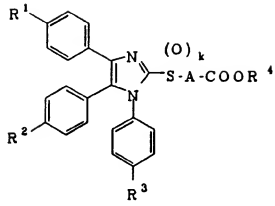


wherein

R^1, R^2, R^3, R^4, R^5 and R^6	independently are H, F, Cl, Br, I, alkyl, alkoxy, or CF_3, with the proviso that one or several of R^1 and R^2, R^3 and R^4, or R^5 and R^6 taken together represent methylenedioxy;
R^7	is H, alkali metal ion, alkyl of 1 to 6 carbon atoms, or benzyl; and
n	is 0 to 10.

The synthesis and the use of these compounds in the treatment of thromboembolic, inflammatory and/or atherosclerotic diseases is disclosed.

U.S. Patent No. 4,654,358, issued to Lautenschläger et al. on March 31, 1987, discloses compounds of the formula:



wherein

k is 0, 1, or 2,

R^1, R^2 and R^3 independently are H, F, Cl, CH_3, CH_3O, or CF_3;

R^4 is H, Na, K, CH_3, CH_3CH_2, $(CH_3)_2CH$, $CH_3(CH_2)_2$, or butyl;

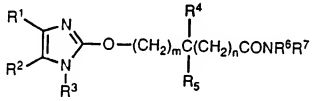
A is $C(CH_3)_2$, $CH(CH_2)_mCH_3$, $(CH_2)_n$, or $(CH_2)_{n-2}(CH(CH_3)$;

m is 0 to 8; and

n is 2 to 10.

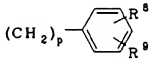
The synthesis and the use of these compounds in the treatment of inflammatory diseases, diseases of lipid metabolism, and/or hyperlipidemic diseases is disclosed.

German Laid Open Application No. DE 3504679, Lautenschläger et al., published August 14, 1986, discloses compounds of the formula:



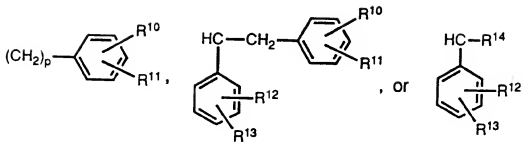
wherein

R^1, R^2 and R^3 independently are H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 1 to 6 carbon atoms, or



R^4 and R^5 independently are H, C_6H_5, or alkyl of 1 to 9 carbon atoms;

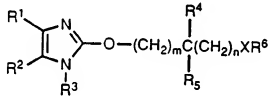
R^6 and R^7 independently are H, OH, saturated or unsaturated alkyl, cycloalkyl, or hydroxyalkyl of 1 to 10 carbon atoms,



R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13}	independently are H, F, Cl, Br, NO_2, CH_3CONH, OH, alkyl of 1 to 3 carbon atoms, CF_3, and alkoxy of 1 to 3 carbon atoms, with the proviso that R^8 and R^9, R^{10} and R^{11}, or R^{12} and R^{13} taken together represent methylenedioxy;
R^{14}	is alkyl of 1 to 2 carbon atoms;
m and n	taken together represent a whole number from 0 to 9;
p	is 0 to 2;
s	is 0 to 2; and
t	is 0 or 2.

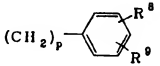
The synthesis and the use of these compounds in the treatment of thromboembolic, inflammatory, atherosclerotic, and lipid metabolism diseases in general is disclosed.

German Laid Open Application No. DE 3504680, Lautenschläger et al., published August 4, 1986, discloses compounds of the formula:



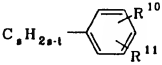
wherein

R^1, R^2 and R^3	independently are H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 1 to 6 carbon atoms, or



R^1 and R^2 can be taken together with the carbon atoms in the 4 and 5 position of the imidazole ring to represent a carbocyclic five- or six-membered aromatic or partially hydrogenated ring which may be substituted by R^8 or R^9;

R^4 and R^5	independently are H, C_6H_5, or alkyl of 1 to 9 carbon atoms;
R^6	is alkyl, cycloalkyl, or hydroxyalkyl of 1 to 20 carbon atoms, H, alkali metal if X is -COO-, 1-phenethyl, or



R^7	is H, OH if X is -CONR^7-, or alkyl of 1 to 4 carbon atoms;
R^8, R^9, R^{10} and R^{11}	are independently H, Cl, F, Br, NO_2, CH_3CONH, OH, alkyl of 1 to 3 carbon atoms, CF_3, or alkoxy of 1 to 3 carbons, or R^8 and R^9 or R^{10} and R^{11} taken together represent methylenedioxy;
X	is a bond, O, OC(=O)O, C(=O)O, CONR^7, OC(=O), or OC(=O)NR^7;
m and n	taken together represent a whole number from 0 to 9;
p	is 0 to 2;
s	is 0 to 2; and
t	is 0 or 2.

The synthesis and the use of these compounds in the treatment of thromboembolic, inflammatory, atherosclerotic, and lipid metabolism diseases in general is disclosed.

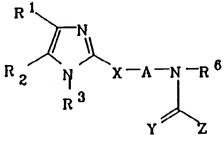
There are no known literature references disclosing the imidazoles of this invention, their use as ACAT inhibitors, or their use in the treatment of atherosclerosis.

The compounds of this invention are very potent ACAT inhibitors. As shown by the data presented below in Table 6, the compounds of this invention inhibit ACAT activity in vitro with at least ten times the potency of any ACAT inhibitors described in the current literature. As shown by the data presented below in Table 8, the compounds of this invention cause a reduction in the serum cholesterol level in cholesterol-fed hamsters. The compounds of this invention are thus expected to be useful in pharmaceutical formulations for the treatment of atherosclerosis. The compounds of this invention have been shown to lower serum cholesterol, and this invention should not be construed as limited to any particular antihypercholesterolemic mechanism of action.

Summary of the Invention

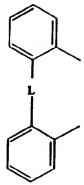
The present invention provides novel compounds of Formula (I), processes for their preparation, pharmaceutical compositions containing such imidazoles, and therapeutic methods for their use as antihypercholesterolemic agents.

This invention provides compounds of Formula (I):



wherein

R^1 and R^2	are selected independently from H, C_1-C_8 alkyl, provided that when R^1 is H, then R^2 cannot be H and when R^1 is C_1-C_8 alkyl, then R^2 cannot be C_1-C_8 alkyl, C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_7-C_{14} araalkyl, 2-, 3- or 4-pyridinyl, 2-thienyl, 2-furanyl, phenyl optionally substituted with 1 to 3 groups selected from F, Cl, Br, OH, C_1-C_4 alkoxy, C_1-C_4 alkyl, C_3-C_8 branched alkyl, $CH_3S(O)_t$, NO_2, CF_3, or NR^7R^8; or
R^1 and R^2	can also be taken together as



where L or O, $O(CH_2)_{m+1}O$, or $(CH_2)_m$ where m is 0-4;

R^3 is H, C_1-C_6 alkyl, allyl, benzyl, or phenyl optionally substituted with F, Cl, CH_3, CH_3O, or CF_3;

R^4 is straight chain C_1-C_8 alkyl optionally substituted with F; C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_7-C_{14} araalkyl where the aryl group is optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl or alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8, or $NCOR^7$; C_3-C_6 alkenyl or alkynyl, C_1-C_3 perfluoroalkyl, phenyl optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl,C_1-C_4 alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8 or $NCOR^7$; pentafluorophenyl, benzyl optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl or alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8, or $NCOR^7$; 2-, 3- or 4-pyridinyl, pyrimidinyl, or biphenyl;

R^5 is H, C_1-C_5 alkyl, or benzyl;

R^6 is H, C_1-C_8 alkyl, C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, C_3-C_8 alkenyl or alkynyl, phenyl optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl or alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8, or $NCOR^7$; pentafluorophenyl, benzyl optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl or alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8, or $NCOR^7$;

R^7 and R^8 are selected independently from H or C_1-C_4 alkyl;

X is $S(O)_n$, O, NR^5, CH_2;

A is C_2-C_{10} alkyl, C_3-C_{10} branched alkyl, C_3-C_{10} alkenyl, or C_3-C_{10} alkynyl;

Y is O, S, H_2;

Z is NHR^4, OR^4, or R^4;

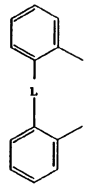
r is 0-2,

or a pharmaceutically acceptable salt thereof.

Preferred are compounds of Formula (I) wherein:

R^1 and R^2 are selected independently from C_1-C_8 alkyl, provided that when R^1 is C_1-C_8 alkyl, then R^2 cannot be C_1-C_8 alkyl, C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_7-C_{14} araalkyl, 2-, 3-, or 4-pyridinyl, 2-thienyl, 2-furanyl, phenyl optionally substituted with 1 to 2 groups selected from F, Cl, Br, OH, C_1-C_4 alkoxy, C_1-C_4 alkyl, C_3-C_5 branched alkyl, $CH_3S(O)_n$, NO_2, CF_3, or NR^7R^8; or

R^1 and R^2 can also be taken together as



where L is O, $O(CH_2)_{m+1}O$, or $(CH_2)_m$ where m is 0-4. More preferred are compounds of Formula (I) wherein:

R^3 is H, CH_3, phenyl;

R^6 is H, C_1-C_8 alkyl, C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, phenyl optionally substituted with 1 to 3 groups selected from CH_3, CH_3O, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, or di(C_1-C_4)alkylamino; or benzyl optionally substituted with 1 to 3 groups selected from CH_3, CH_3O, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, or di(C_1-C_4)alkylamino;

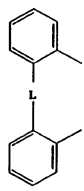
X is S(O)r, CH_2;

A is C_2-C_{10} alkyl, C_4-C_9 branched alkyl.

More specifically preferred because of their biological activity are compounds of Formula (I) wherein:

R^1 and R^2 are selected independently from C_1-C_8 alkyl, provided that when R^1 is C_1-C_8 alkyl, then R^2 cannot be C_1-C_8 alkyl, C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_7-C_{14} araalkyl, 2-, 3-, or 4-pyridinyl, 2-thienyl, or phenyl optionally substituted with 1 to 2 groups selected from F, Br, Cl, C_1-C_4 alkyl, C_3-C_8 branched alkyl, CH_3O, $CH_3S(O)_r$, NO_2, CF_3, or di(C_1-C_4)alkylamino; or

R^1 and R^2 can also be taken together as



where L is O or OCH_2O;

R^3 is H;

R^4 is C_1-C_8 alkyl, C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_7-C_{14} araalkyl, phenyl substituted with 1 to 3 groups selected from CH_3, F, Cl, CH_3O, CN; or benzyl optionally substituted with 1 to 3 groups selected from CH_3, CH_3O, F, Cl, or CN;

R^6 is C_1-C_8 alkyl or phenyl optionally substituted with 1 to 3 groups selected from CH_3, CH_3O, F, Cl, or CN;

A is C_4-C_9 alkyl;

X is $S(O)_r$;

Y is O, H_2.

Specifically preferred are:

N'-(2,4-difluorophenyl)-N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptylurea

N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptyl-N'-phenylurea

N'-(2,4-difluorophenyl)-N-[8-(4,5-diphenyl-1H-imidazol-2-ylthio)octyl]-N-heptylurea
N-butyl-N'-(2,4-difluorophenyl)-N-[8-(4,5-diphenyl-1H-imidazol-2-ylthio)octyl]urea
N'-(2,4-dimethoxyphenyl)-N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptylurea
N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptyl-N'-methylurea
N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptyl-N'-propylurea
N'-(2,4-difluorophenyl)-N-[5-[4,5-diphenyl)-1H-imidazol-2-yl)sulfonyl]pentyl]-N-heptylurea
N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N'-(3-fluorophenyl)-N-heptylthiourea
N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N'-(3-fluorophenyl)-N-heptylurea
N'-(2,4-difluorophenyl)-N-heptyl-N-[5-(4-phenyl-1H-imidazol-2-ylthio)pentyl]urea
N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptyl-N'-(2,4,6-trifluorophenyl)thiourea
N'-(2,6-dichlorophenyl)-N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptylurea
N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptyl-N'-(1-methylethyl)urea
N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-2,4-difluoro-N-heptylbenzeneacetamide
N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptyl-N'-propylthiourea
N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptyl-N'-octylurea
N'-cyclohexyl-N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptylurea
N'-(2,4-difluorophenyl)-N-[5-(4,5-diphenyl-1H-imidazol-2-yl)sulfinyl]pentyl]-N-heptylurea
N'-(2,4-difluorophenyl)-N-[2-(4,5-diphenyl-1H-imidazol-2-ylthio)ethyl]-N-heptylurea
N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptylbutanamide
N-[5-(4,5-bis(4-methoxyphenyl)-1H-imidazol-2-ylthio]pentyl]-N'-(2,4-difluorophenyl)-N-heptylurea
N-[5-[4,5-bis(1-methylethyl)-1H-imidazol-2-ylthio]pentyl]-N'-(2,4-difluorophenyl)-N-heptylurea
N'-(2,4-difluorophenyl)-N-[5-(4,5-dipropyl-1H-imidazol-2-ylthio)pentyl]-N-heptylurea
N-[5-[4,5-bis(4-fluorophenyl)-1H-imidazol-2-ylthio]pentyl]-N'-(2,4-difluorophenyl)-N-heptylurea
N-[5-(1H-dibenz[2,3:6,7]oxedino[4,5-d]imidazol-2-ylthio)pentyl]-N'-(2,4-difluorophenyl)-N-heptylurea
N-[5-[4,5-bis(2-thienyl)-1H-imidazol-2-ylthio]pentyl]-N'-(2,4-difluorophenyl)-N-heptylurea
N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptylpentanamide
N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptyl[1,1'-biphenyl]-4-acetamide
N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptyl-N'-(2,4,6-trifluorophenyl)urea
N-[5-[4,5-bis(2-pyridinyl)-1H-imidazol-2-ylthio]pentyl]-N'-(2,4-difluorophenyl)-N-heptylurea
N'-(2,4-difluorophenyl)-N-[6-(4,5-diphenyl)-1H-imidazol-2-yl)hexyl]-N-heptylurea
N-[5-[4,5-bis(4-methylphenyl)-1H-imidazol-2-ylthio]pentyl]-N'-(2,4-difluorophenyl)-N-heptylurea
N-[5-[4,5-bis(4-methoxyphenyl)-1H-imidazol-2-ylthio]pentyl]-N-heptylbutanamide
N-[5-[4,5-bis(4-hydroxyphenyl)-1H-imidazol-2-ylthio]pentyl]-N'-(2,4-difluorophenyl)-N-heptylurea
N-[5-[4,5-bis(1-methylethyl)-1H-imidazol-2-ylthio]pentyl]-N-heptylcyclohexaneacetamide
N-[5-[4,5-bis(3-methoxyphenyl)-1H-imidazol-2-ylthio]pentyl]-N'-(2,4-difluorophenyl)-N-heptylurea
N-[5-[4,5-bis(2-methoxyphenyl)-1H-imidazol-2-ylthio]pentyl]-N'-(2,4-difluorophenyl)-N-heptylurea
N'-[1,1'-biphenyl)-4-yl]-N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptylurea
N-(2,4-difluorophenyl)-N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N'-octylurea
Propyl [5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]heptylcarbamate
(Phenylmethyl) [5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]heptylcarbamate
Phenyl [5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]heptylcarbamate
(2-Methylpropyl) [5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]heptylcarbamate
Ethyl [5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]heptylcarbamate
Octyl [5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]heptylcarbamate
N-[5-[4,5-bis[4-(dimethylamino)phenyl]-1H-imidazol-2-ylthio]pentyl]-N'-(2,4-difluorophenyl)-N-heptylurea
N-[5-(4,5-dicyclohexyl-1H-imidazol-2-ylthio)pentyl]-N'-(2,4-difluorophenyl)-N-heptylurea)
(4-fluorophenyl)[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]heptylcarbamate
N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N'-octyl-N-phenylurea
N-[5-(1H,9H-dibenz[4,5:8,9][1,3]dioxonino[6,7-d]imidazol-2-ylthio)-pentyl-N'-(2,4-difluorophenyl)-N-heptylurea
N'-(4-cyanophenyl)-N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptylurea
N-(2,4-difluorophenyl)-N'-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]urea
N-[5-[4,5-bis(4-methoxyphenyl)-1H-imidazol-2-ylthio]pentyl]-2,4-difluoro-N-heptylbenzeneacetamide
Phenyl [5-[4,5-bis(4-dimethylamino)phenyl)-1H-imidazol-2-ylthio]pentyl]heptylcarbamate
or pharmaceutically acceptable salts thereof.

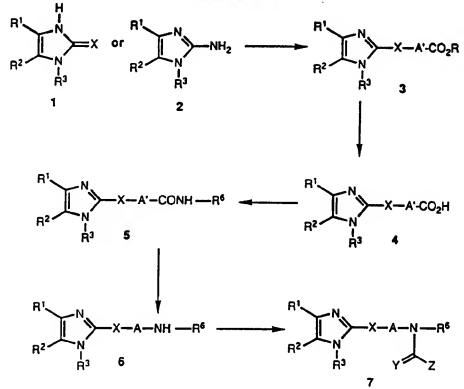
Detailed Description of the Invention

Synthesis

The novel compounds of Formula (I) may be prepared using the reactions and techniques described in this section. The reactions are performed in solvents appropriate to the reagents and materials employed and suitable for the transformation being effected. It is understood by those skilled in the art of organic synthesis that the functionality present on the imidazole and other portions of the molecule must be compatible with the reagents and reaction conditions proposed. Not all compounds of Formula (I) falling into a given class may be compatible with some of the reaction conditions required in some of the methods described. Such restrictions to the substituents which are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternative methods described must then be used.

The compounds of Formula (I) wherein X is O, S, CH_2 or NH can be prepared by the route shown in Scheme 1. The esters of Formula (3) wherein X is O or S can be prepared by converting the requisite 4-imidazolin-2-one (1) where X is O, or 4-imidazolin-2-thione (1) where X is S, into the corresponding alkali metal salt by addition of a base such as sodium hydride, and the salt is alkylated with a compound of the formula M-(A')CO_2R, wherein R is CH_3 or C_2H_5, M is a halogen or a tosylate group, and A' is a moiety having one less methylene group than A, in a polar solvent such as N,N-dimethylformamide. Alternatively, the esters of Formula (3) where X is S may be prepared by direct alkylation of the requisite 4-imidazolin-2-thione with M-(A')CO_2R, without the addition of a suitable base, in a polar solvent such as N,N-dimethylformamide at a temperature from ambient temperature to the reflux temperature of the solvent. The esters of Formula (3) wherein X is NH can be prepared by the reaction of the requisite 2-aminoimidazole of Formula (2) with a compound of the formula M-(A')CO_2R wherein R, M, and A' are as defined above, in a suitable solvent such as N,N-dimethylformamide. Compounds of Formula (2) wherein R^3 is H are preferentially alkylated at a ring nitrogen atom. Therefore, in order to prepare compounds of Formula (I) wherein X is NH and R^3 is H, it is usually necessary to protect the ring nitrogen atom. The protecting group is preferably stable under basic conditions and easily removed under acidic conditions, e.g., a silyl or trityl group. The protected 2-aminoimidazole can then be used to prepare esters of Formula (3) wherein R^3 is a protecting group. The protecting group can be removed at any suitable stage in the synthetic sequence for the preparation of the compounds of Formula (I) wherein X is NH and R^3 is H.

Scheme 1



The esters of Formula (3) are hydrolyzed to the corresponding carboxylic acids of formula (4) by methods which are well known in the chemical literature. For example, the hydrolysis can be accomplished by reaction with an alkali metal hydroxide in aqueous or organic solvents such as water, alcohols, ethers or mixtures thereof, followed by acidification with a mineral acid. The methods used to prepare compounds of formula (4) are substantially similar to the methods described in U.S. 4,654,358, U.S. 4,460,598 and in U.S. 4,900,744. Compounds of Formula (4) wherein R^1 and R^2 are phenyl or substituted phenyl, R^3 is H, X is S, A' is $(CH_2)_{n-1}$ and n is 8 to 21 are claimed as antihypercholesterolemic compounds in U.S. 4,900,744.

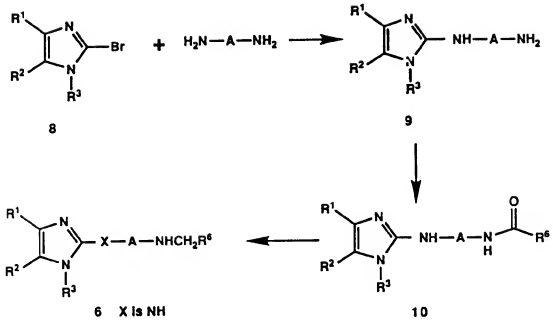
The amides of Formula (5) are prepared by coupling the carboxylic acids of Formula (4) with a primary amine by amide bond forming reactions which are well known in the chemical literature. One method of amide bond formation is to use a coupling reagent which generates a reactive intermediate such as a mixed anhydride or active ester. Examples of such coupling agents are disubstituted carbodiimides, N,N'-carbonyldiimidazole, diphenylphosphoryl azide, and the like. For example, the coupling can be carried out with a disubstituted carbodiimide such as dicyclohexylcarbodiimide in an appropriate solvent such as methylene chloride, acetonitrile, toluene, or N,N-dimethylformamide. Nucleophilic hydroxy compounds such as 1-hydroxy-1H-benzotriazole, which form highly active esters, may be added to catalyze the reaction.

There are several alternate approaches to the preparation of the amides of Formula (5). For example, the boron trifluoride etherate catalyzed reaction of the carboxylic acids of Formula (4) with a primary amine, with azeotropic removal of water, affords the amides of Formula (5). Another approach is to convert the carboxylic acids of Formula (4) to the corresponding acid chloride using thionyl chloride, oxalyl chloride or the like and then to react the acid chloride with a primary amine in the presence of a base such as triethylamine to afford the amides of Formula (5). Alternatively, the esters of Formula (3) can be directly converted to the amides of Formula (5) by ester aminolysis in the presence of strong alkali metal catalysts such as sodium amide, sodium hydride, sodium methoxide, Grignard reagents or butyllithium, or in the presence of milder catalysts such as 2-pyridone, boron tribromide, or dimethylaluminum amides.

The amines of Formula (6) can be prepared by reduction of the corresponding amides of Formula (5) by a variety of methods well known to those skilled in the art. For example, reagents such as lithium aluminum hydride, diborane, sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al®), and diisobutylaluminum hydride can be used to reduce an amide to an amine. Such reactions are typically conducted in an appropriate anhydrous aprotic solvent such as ether, toluene or tetrahydrofuran at a temperature from room temperature to the boiling point of the solvent for a period of 2-48 hours.

Alternatively amines of Formula (6), wherein X is NH can be prepared by the route shown in Scheme 2. The primary amines (9) can be prepared by reacting 2-bromoimidazoles of Formula (8) with an appropriately elaborated diamine under neat, thermal conditions or in appropriate solvent such as N,N-dimethylformamide, toluene, acetonitrile or tetrahydrofuran, at or below the boiling point of the solvent.

Scheme 2



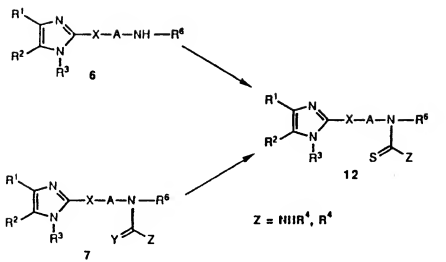
The secondary amines of Formula (6) wherein X is NH can be prepared by direct alkylation of the primary amines of Formula (9) with an appropriately substituted alkyl halide. Or, the secondary amines (6) are prepared by acylation of the primary amines of Formula (9) with an acid chloride or activated carboxylic acid derivative to give the amide of Formula (10) and reduction of the amide (10) to the amines (6) by well known methods previously described.

The compounds of Formula (7) where Y is O and Z is NR^4, OR^4 R^4 are prepared by the reaction of the secondary amines (6) with the requisite isocyanates, chloroformates, acid chlorides or activated carboxylic acid derivatives in an appropriate solvent such as hexane, toluene, diethyl ether, methylene chloride or tetrahydrofuran at a temperature at or below the boiling point of the solvent.

The amines of Formula (7), wherein Y is H_2 are prepared by reaction of the corresponding ureas or amides of Formula (7) wherein Y is O, with a reducing agent such as lithium aluminum hydride or other such reagents in an appropriate anhydrous aprotic solvent such as hexane, toluene, diethylether or tetrahydrofuran at temperatures at or below the boiling point of the solvent.

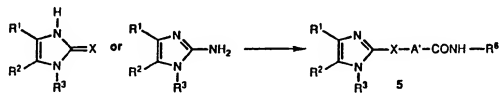
As shown in Scheme 3, the thioureas of Formula (12) wherein X is S, O or NH and Z is NHR^4 can be prepared in an analogous manner by the reaction of the secondary amines of Formula (6) with the requisite isothiocyanate. Alternatively, the thioureas or thioamides where Z is R^4 of Formula (12) can be prepared from the ureas or amides of Formula (7) by the reaction with Lawesson's reagent or diphosphorus pentasulfide in an appropriate solvent such as toluene.

Scheme 3



As shown in Scheme 4, alternatively the amides of Formula (5) can be prepared by the alkylation of (1) or (2) with compounds of the formula M-(A')CONHR^6 wherein M is a halogen or tosylate group, as, described for compounds of Formula (3), Scheme 1.

Scheme 4



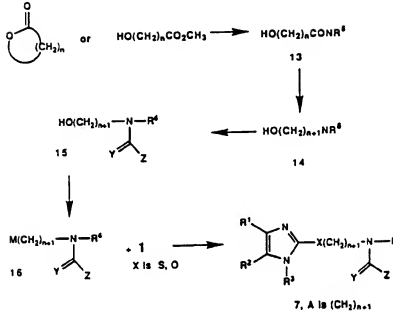
Alternatively, compounds of Formula (7), where X is O, S, or NH can be prepared by the route shown in Scheme 5. The compounds of Formula (13) can be prepared from a lactone or an hydroxyalkylcarboxylic ester and an appropriate amine, neat or in an inert solvent such as N,N-dimethylformamide at ambient or elevated temperatures. The amines of Formula (14) are prepared by reduction of the corresponding amide of Formula (13) by a variety of well known methods, as illustrated above. The compounds of Formula (15) are prepared by the reaction of the secondary amine (14) with the requisite isocyanates, chloroformates, acid chlorides or activated carboxylic acid derivatives as described for the preparation of compounds of Formula (7), Scheme 1.

The compound of Formula (16) can be prepared by conversion of the hydroxy group to a halogen moiety by a variety of well known methods. Examples of these methods are phosphorous tribromide, phosphorous oxychloride, thionyl chloride, or triphenylphosphine and carbon tetrabromide. Or, compounds of Formula (16) where M is a tosylate or similar functionality, can be prepared from toluene sulfonyl chloride and triethylamine, in an appropriate aprotic solvent such as methylene chloride, tetrahydrofuran or toluene.

The compounds of Formula (7) can be prepared by converting the requisite 4-imidazolin-2-one (1) where X is O, or 4-imidazoline-2-thione (1) where X is S into the corresponding alkali metal salt by addition of a base such as sodium hydride, and alkylating with the compounds of Formula (16) in a polar aprotic

solvent such as N,N-dimethylformamide at an appropriate temperature.

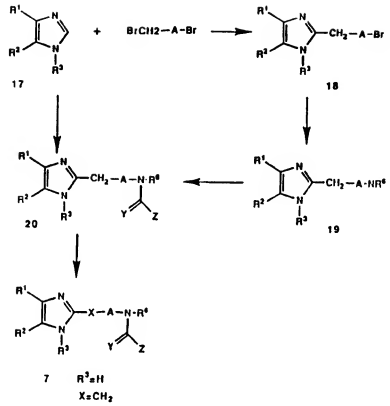
Scheme 5



The compounds of Formula (7) wherein X is CH_2 are prepared by the route shown in Scheme 6. The compounds of Formula (18) are prepared by converting the requisite imidazoles of Formula (17) where R^3 is alkyl or an appropriate protecting group, into the corresponding alkali metal salt, by addition of a base such as n-butyl lithium, and alkylating with an appropriate alkyl halide in a solvent such as tetrahydrofuran under an inert atmosphere and reduced temperatures. The compounds of Formula (19) are prepared from compounds of Formula (18) by reaction with an appropriately substituted amine, in an inert solvent such as toluene, acetonitrile, tetrahydrofuran or N,N-dimethylformamide, at a temperature at or below the boiling point of the solvent. The imidazole compounds of Formula (20) are prepared by the reaction of the secondary amines of Formula (19) with the requisite isocyanate, chloroformate, acid chloride or other activated carboxylic acid derivative as previously described. Or, the imidazole compounds of Formula (20) can be prepared by reacting the alkali metal salt of compounds of Formula (17) with the elaborated compounds of Formula (16) in analogous conditions described above. The compounds of Formula (7) wherein X is CH_2 and R^3 is H, are prepared by deprotecting compounds of Formula (20), where R^3 is a protecting group. For example, when R^3 is a silyl protecting group, removal with tetrabutylammonium fluoride in tetrahydrofuran at reflux, affords compounds of Formula (7) where X is CH_2.

Likewise, compounds of Formula (7) wherein X is O, S, NH or CH_2 and Y is H_2 may be prepared by reacting compounds similar to compounds of Formula (18) with an appropriately functionalized secondary amine, $HNCH_2ZR^6$, in a solvent such as toluene, acetonitrile, tetrahydrofuran, or N,N-dimethylformamide at a temperature at or below the boiling point of the solvent.

Scheme 6

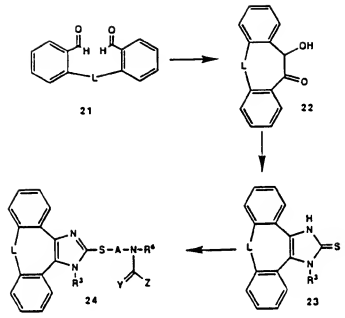


The linked phenyl compounds of Formula (24) are prepared as shown in Scheme 7. The linked bis-benzaldehyde compounds of Formula (21) are prepared by bis alkylation of an appropriately functionalized dihaloalkyl, with a substituted salisaldehyde, using an alkali base, such as sodium hydride in an inert solvent, such as N,N-dimethylformamide. The α-hydroxyketones of Formula (22) are prepared by standard literature benzoin forming reaction conditions, Walter S. Ide, Johannes S. Buck, Organic Reactions, Vol. IV, p. 269, utilizing potassium cyanide in ethanol:water, at reflux.

The imidazoles of Formula (23) are prepared by methods well known in the literature, Klaus Hoffman, The Chemistry of Heterocyclic Compounds, Imidazoles, Part I, by condensing the α-hydroxyketone compounds of Formula (22) with thiourea, or ammonium thiocyanate, or an appropriately substituted thiourea in a suitable solvent such as N,N-dimethylformamide, ethanol or hexanol, at a temperature at or below the boiling point of the solvent.

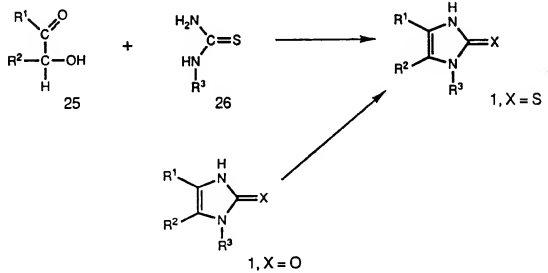
The compounds of Formula (24) are prepared by alkylating the alkali metal salt of imidazole (23) with the compound of Formula (16), as described previously to give the compounds of Formula (24) directly or with compound of formula $M(A')CO_2R$ when R is CH_3 or C_2H_5, M is halogen or a tosylate group and A' is a moiety having one less methylene group than A, as described in Scheme 1.

Scheme 7



The compounds of Formula (1), Scheme 8, wherein X is S are available from commercial sources or can be prepared by methods as described above.

Scheme 8

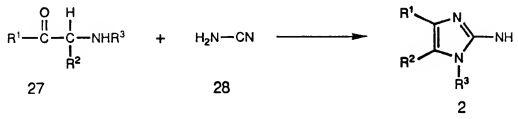


Alternatively, the compounds of Formula (1) where X is S, Scheme 8, can be prepared from the corresponding 4-imidazolin-2-ones of Formula (1) where X is O, Org. Syn. Coll., Vol. II, 231, by reaction with Lawesson's reagent or diphosphorus pentasulfide in a suitable solvent such as toluene.

As shown in Scheme 9, the 2-aminoimidazoles of Formula (2) can be prepared by the reaction of the appropriately substituted α-aminoketones of Formula (27) with cyanamide (28). Compounds of Formula (2)

can be used in the preparation of compounds of Formula (I) as previously described in Scheme 1.

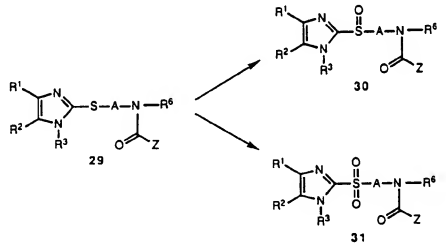
Scheme 9



27 28 2

As shown in Scheme 10, the compounds of Formula (I) wherein X is $S(O)_r$ and r is 1 or 2 can be prepared by the oxidation of the compounds of Formula (29) by methods which are well known in the chemical literature. For example, the oxidation of (29) with one equivalent of a peracid such as m-chloroperoxybenzoic acid in a suitable solvent such as methylene chloride at a low temperature affords primarily the sulfoxides of Formula (30), and the oxidation of (29) with an oxidant such as potassium hydrogen persulfate, or Oxone®, in a suitable solvent such as methanol affords the sulfones of Formula (31).

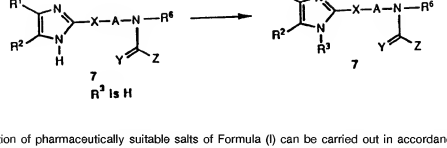
Scheme 10



29 30 31

Alternatively, compounds of Formula (7) where R^3 is not H, Scheme 11, can be prepared by direct alkylation of compounds of Formula (7) when R is H, in the presence or absence of a base such as potassium carbonate, pyridine, sodium hydride, triethylamine, or potassium t-butoxide in an appropriate solvent such as N,N-dimethylformamide, glyme, tetrahydrofuran, pyridine or methylene chloride.

Scheme 11



Preparation of pharmaceutically suitable salts of Formula (I) can be carried out in accordance with well known techniques for forming salts. Physiologically acceptable salts include acid addition salts, e.g., hydrochloric, sulfuric, acetic, trifluoroacetic, succinic, citric, and benzene sulfonic acid salts.

The compounds of this invention and their preparation can be further understood by the following examples, which exemplify but do not constitute a limitation of the invention. In these examples, unless otherwise indicated, all temperatures are in degrees centigrade and parts and percentages are by weight.

EXAMPLE 1

Preparation of N'-(2,4-difluorophenyl)-N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptylurea

Part A. To a solution of 4,5-diphenyl-2-imidazolethiol (25.2 g, 0.1 mol) in N,N-dimethylformamide (250 ml) was added, dropwise, a solution of ethyl 5-bromopentanoate (23.73 mL, 31.35 g, 0.15 mol) in N,N-dimethylformamide (80 mL), and the reaction mixture was stirred at reflux under nitrogen for 18 hours. The reaction mixture was cooled, poured into 5% sodium bicarbonate and ice, and then extracted with ethyl acetate. The combined organic extracts were washed sequentially with 5% sodium bicarbonate, water, saturated sodium chloride solution, dried over magnesium sulfate, and concentrated under vacuum. The residue was chromatographed with 7:3 hexane-ethyl acetate, and the resulting solid was recrystallized from acetonitrile and triturated with hexane to give 5-(4,5-diphenyl-1H-imidazol-2-ylthio)-pentanoic acid ethyl ester (25.95 g, 0.068 mol) as a white solid, mp 87-89°. ^{1}H NMR (DMSO-d_6) δ 7.55-7.15(m,11H), 4.0(q,2H,J = 8Hz), 2.9(t,2H,J-7Hz), 2.3(t,2H,J = 7Hz), 1.9-1.6(m,4H), 1.2(t,3H,J = 8Hz).

Additional esters which can be used as intermediates in the preparation of compounds of Formula (I) are prepared similarly as taught in U.S. 4,900,744.

Part B. To a solution of 5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentanoic acid ethyl ester (7.6 g, 0.02 mol) in ethanol (200 mL), was added dropwise a solution of sodium hydroxide (7.6 g) in water (200 mL), and the reaction mixture was stirred at reflux under nitrogen for 3 hours. The reaction mixture was concentrated to half the original volume and then extracted with ether. The ether extracts were discarded. The reaction mixture was acidified to pH 1 with 1 N hydrochloric acid and extracted with ether, and the combined organic extracts were dried over magnesium sulfate and concentrated under vacuum. The resulting solid was recrystallized from acetonitrile and triturated with hexane to give 5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentanoic acid (3.88 g, 0.011 mol) as a white solid, mp 190-195°. ^{1}H NMR (DMSO-d_6) δ 12.6(s,1H), 7.6-7.1(m,10H), 3.3-3.1(m,2H), 2.3-2.1(m,3H), 1.8-1.6(m,4H).

Additional acids which can be used as intermediates in the preparation of compounds of Formula (I) are prepared similarly and are claimed in U.S. 4,900,744.

Part C, Method 1. To a solution of 5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentanoic acid (2.0 g, 0.0057 mol) in N,N-dimethylformamide (25 mL) was added 1-hydroxybenzotriazole hydrate (0.93 g, 0.0069 mol) followed by a solution of heptylamine (1.10 mL, 0.86 g, 0.0074 mol) in N,N-dimethylformamide (10 mL). The reaction mixture was cooled to 0° and dicyclohexylcarbodiimide (1.42 g, 0.0069 mol) was added portionwise as a solid. The reaction mixture was stirred for 2 hours at 0° and then stirred for 48 hours at ambient temperature. The solids were filtered and washed with N,N-dimethylformamide. The filtrate was concentrated and the residue was chromatographed with 1:1 hexane-ethyl acetate. The resulting solid was recrystallized from acetonitrile and triturated with hexane to give 5-(4,5-diphenyl-1H-imidazol-2-ylthio)-N-heptylpentanamide (2.21 g, 0.0049 mol) as a white solid, mp 104-106°. ^{1}H NMR ($CDCl_3$) δ

11.6(s,1H), 7.6-7.1(m,10H), 6.1-6.0(m,1H), 3.1-2.8(m,4H), 2.2(t,2H,J = 7Hz), 1.9-1.7(m,2H), 1.7-1.5(m,2H), 1.4-1.1(m,10H), 0.9(t,3H,J = 8Hz).

Part C, Method 2. To a solution of 5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentanoic acid (2.0 g, 0.0057 mol) in toluene (35 ml) was added heptylamine (1.63 ml., 1.27 g, 0.011 mol) and then boron trifluoride etherate (1.35 mL., 1.56 g, 0.011 mol) and the reaction mixture was stirred at reflux for 120 hours using a Dean-Stark moisture trap. The reaction mixture was cooled, extracted with 0.1 N NaOH, 0.1 N HCl, and water, and the combined organic extracts were dried over magnesium sulfate and concentrated under vacuum. The residue was chromatographed and worked-up as described in Part C, Method 1, to give 5-(4,5-diphenyl-1H-imidazol-2-ylthio)-N-heptylpentanamide (2.35 g, 0.005 mol) as a white solid.

Part D. To a solution of lithium aluminum hydride, (1.52 g, 0.04 mol) in dry tetrahydrofuran (50 mL) was added, dropwise, a solution of 5-(4,5-diphenyl-1H-imidazol-2-ylthio)-N-heptylpentanamide(4.04 g, 0.009 mol) in tetrahydrofuran (25 mL) and the reaction mixture was stirred at reflux for 18 hours. The reaction mixture was cooled to 0°, quenched by the slow and careful sequential addition of water (1.52 mL), 15% sodium hydroxide (4.56 mL), and water (4.56 mL), and then stirred at 0° for 30 minutes. The solution was then dried over magnesium sulfate and concentrated under vacuum, and the residue was chromatographed with a gradient of 1:0 to 3:1 to 1:1 ethyl acetate-methanol. The resulting yellow oil was triturated with cold hexane to give N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-1-heptanamine as a white solid. A solution of this amine (0.80 g, 0.0018 mol) in ether (20 mL) was treated with a sufficient amount of ethereal HCl (about 25 mL) to cause complete precipitation of the amine as the hydrochloride salt. The reaction mixture was stirred for 15 minutes, and the supernatant liquid was decanted to afford a gummy solid, which was triturated with hot acetonitrile and then with cold hexane to give N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-1-heptanamine hydrochloride (0.82 g, 0.0017 mol) as a white solid, mp 187-190°. ^{1}H NMR ($CDCl_3$) δ 9.3(s,2H), 7.7-7.3(m,10H), 3.7-3.5(m,2H), 3.0-2.7(m,4H), 2.0-1.2(m,16H), 0.9(t,3H,J = 8Hz).

Part E. To a solution of N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-1-heptanamine (1.0 g, 0.0024 mol) in hexane (50 mL) was added, dropwise, a solution of 2,4-difluorophenylisocyanate (0.296 mL, 0.388 g, 0.0025 mol) in hexane (25 mL), and the reaction mixture was stirred at ambient temperature for 3 hours. The reaction mixture was concentrated under vacuum and the residue was chromatographed with 7:3 hexane-ethyl acetate to give the title compound (0.86 g, 0.0015 mol) as a white solid, mp 96-98°. ^{1}H NMR ($CDCl_3$) δ 10.8(s,1H), 7.7-7.1(m,14H), 3.4(t,2H,J = 7Hz), 3.2(t,2H,J = 7Hz), 3.0(t,2H,J = 7Hz), 1.9-1.4-(m,16H), 0.9(t,3H,J = 8Hz).

EXAMPLE 2

Preparation of N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptyl-N'-phenylurea

To a solution of N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-1-heptanamine (1.0 g, 0.0024 mol) in hexane (50 mL) was added, dropwise, a solution of phenylisocyanate (0.27 mL, 0.298 g, 0.0025 mol) in hexane (25 mL) and the reaction mixture was stirred at ambient temperature for 4 hours. The reaction mixture was concentrated under vacuum and the residue was chromatographed with 6:4 hexane-ethyl acetate to give the title compound (0.5 g, 0.009 mol) as a yellow amorphous solid. ^{1}H NMR ($CDCl_3$) δ 11.0-(s,1H), 7.7-6.9(m,14H), 6.4(s,1H), 3.4(t,2H,J = 7Hz), 3.2(t,2H,J = 7Hz), 3.0(t,2H,J = 7Hz), 1.9-1.1(m,16H), 0.9-(t,3H,J = 8Hz).

EXAMPLE 3

Preparation of N'-(2,4-difluorophenyl)-N-[8-(4,5-diphenyl-1H-imidazol-2-ylthio)octyl]-N-heptylurea

Part A. To a solution of 8-(4,5-diphenyl-1H-imidazol-2-ylthio)octanoic acid (8.44 g, 0.02 mol) in methylene chloride (100 mL) at 0° was added, portionwise as a solid, dicyclohexylcarbodiimide (4.12 g, 0.02 mol), and the reaction mixture was stirred at 0° for 30 minutes. To this reaction mixture was added, dropwise, heptylamine (2.96 mL, 2.3 g, 0.02 mol) and the reaction mixture was stirred at reflux for 72 hours. The reaction mixture was cooled, and the solids were filtered and washed with chloroform. The filtrate was concentrated under vacuum and the residue was chromatographed with a gradient of 7:3 to 1:1 hexane-ethyl acetate. The resulting solid was recrystallized from acetonitrile and triturated with hexane to give 8-(4,5-diphenyl-1H-imidazol-2-ylthio)-N-heptyloctanamide (3.28 g, 0.0067 mol) as a white solid, mp 119-120°. ^{1}H NMR (DMSO-d_6) δ 12.5(s,1H), 7.8-7.1(m,10H), 3.2-2.9(m,4H), 2.0(t,2H,J = 7Hz), 1.75-1.0-(m,21H), 1.0-0.8(m,3H).

Part B. To a solution of lithium aluminum hydride (0.96 g, 0.025 mol) in dry tetrahydrofuran (30 mL) was added, dropwise, a solution of 8-(4,5-diphenyl-1H-imidazol-2-ylthio)-N-heptyloctanamide (2.82 g, 0.0057 mol) in tetrahydrofuran (15 mL) and the reaction mixture was stirred at reflux for 18 hours. The reaction mixture was cooled to 0°, quenched by the slow and careful sequential addition of water (0.96 mL), 15% sodium hydroxide (2.88 mL), and water (2.88 mL), and then stirred at 0° for 30 minutes. The solution was then dried over magnesium sulfate and concentrated, and the residue was chromatographed with 1:1 hexane:ethyl acetate and then with a gradient of 1:0 to 3:1 to 1:1 ethyl acetate-methanol to give 8-(4,5-diphenyl-1H-imidazol-2-ylthio)-N-heptyl-1-octanamine (1.07 g, 0.0022 mol) as a white solid, mp 87-89°. ^{1}H NMR ($CDCl_3$) δ 7.6-7.2(m,11H), 3.1(t,2H,J = 7Hz), 2.7-2.5(m,2H), 1.8-1.1(m,25H), 0.9-(t,3H,J = 8Hz).

Part C. To a solution of 8-(4,5-diphenyl-1H-imidazol-2-ylthio)-N-heptyl-1-octanamine (0.5 g, 0.001 mol) in hexane (25 mL) was added, dropwise, a solution of 2,4-difluorophenylisocyanate (0.15 mL, 0.194 g, 0.00125 mol) in hexane (10 mL), and the reaction mixture was stirred at ambient temperature for 3 hours. The reaction mixture was concentrated under vacuum and the residue was chromatographed using 8:2 hexane-ethyl acetate to give a solid which was triturated with cold ethyl acetate and then hexane to give the title compound (0.18 g, 0.00028 mol) as a white solid, mp 89-91°. ^{1}H NMR (DMSO-d_6) δ 12.5(s,1H)-,7.9(s,1H), 7.5-7.1(m,10H), 3.3-3.1(m,5H), 1.8-1.2(m,17H), 0.9(t,3H,J = 8Hz).

EXAMPLE 4

Preparation of N-butyl-N'-(2,4-difluorophenyl)-N-[8-(4,5-diphenyl-1H-imidazol-2-ylthio)octyl]urea

Part A. To a solution of 8-(4,5-diphenyl-1H-imidazol-2-ylthio)octanoic acid (4.4 g, 0.0125 mol) in methylene chloride (65 mL) at 0° was added, portionwise as a solid, dicyclohexylcarbodiimide (2.3 g, 0.011 mol) and the reaction mixture was stirred at 0° for 30 minutes. To this reaction mixture was added, dropwise, a solution of butylamine (1.24 mL, 0.92 g, 0.012 mol) in methylene chloride (15 mL) and the reaction mixture was stirred at reflux for 18 hours. The reaction mixture was cooled, and solids were filtered and washed with methylene chloride. The filtrate was concentrated under vacuum and the residue was chromatographed with a gradient of 7:3 to 1:1 hexane-ethyl acetate. The resulting solid was recrystallized from acetonitrile and triturated with hexane to give N-butyl-8-(4,5-diphenyl-1H-imidazol-2-ylthio)octanamide (1.43 g, 0.003 mol) as a white solid, mp 136-137°. ^{1}H NMR (DMSO-d_6) δ 12.5(s,1H), 7.8-7.7(m,1H), 7.7-7.1(m,10H), 3.2-2.9(m,4H), 2.0(t,2H,J = 7Hz), 1.8-1.1(m,14H), 0.9(t,3H,J = 8Hz).

Part B. To a solution of lithium aluminum hydride (0.46 g, 0.012 mol) in dry tetrahydrofuran (15 mL) was added, dropwise, a solution of N-butyl-8-(4,5-diphenyl-1H-imidazol-2-ylthio)octanamide(1.20 g, 0.0027 mol) in tetrahydrofuran (8 mL) and the reaction mixture was stirred at reflux for 18 hours. The reaction mixture was cooled to 0°C and quenched by the slow and careful sequential addition of water (0.46 mL), 15% sodium hydroxide (1.38 mL), and water (1.38 mL) and then the reaction mixture was stirred at 0° for 30 minutes. The solution was dried over magnesium sulfate and concentrated under vacuum, and the residue was chromatographed with 1:1 hexane-ethyl acetate and then with a gradient of 1:0 to 8:2 to 1:1 ethyl acetate-methanol. The resulting solid was triturated with hexane to give N-butyl-8-(4,5-diphenyl-1H-imidazol-2-ylthio)octanamine (0.45 g, 0.001 mol) as a white solid, mp 75-78°. ^{1}H NMR ($CDCl_3$) δ 7.6-7.1-(m,10H), 3.1(t,2H,J = 7Hz), 2.5(t,2H,J = 7Hz), 1.7-1.0(m,16H), 0.9(t,3H,J = 8Hz).

Part C. To a solution of N-butyl-8-(4,5-diphenyl-1H-imidazol-2-ylthio)octanamine (0.2 g, 0.00045 mol) in hexane (15 mL) was added, dropwise, a solution of 2,4-difluorophenylisocyanate (0.065 mL, 0.085 g, 0.00055 mol) in hexane (5 mL) and the reaction mixture was stirred at ambient temperature for 3 hours. The reaction mixture was concentrated under vacuum and the residue was chromatographed with 7:3 hexane-ethyl acetate and the resulting solid was recrystallized from acetonitrile and triturated with hexane to give the title compound (0.138 g, 0.00023 mol) as a white solid, mp 114-115°. ^{1}H NMR ($CDCl_3$) δ 8.1-7.9(m,1H), 7.6-7.2(m,11H), 6.95-6.75(m,2H), 6.5-6.4(m,1H), 3.4-3.1(m,6H), 1.8-1.3(m,16H), 1.0-(t,3H,J = 8Hz).

EXAMPLE 5

Preparation of N'-(2,4-dimethoxyphenyl)-N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptylurea

To a solution of N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-1-heptanamine (0.75 g, 0.0017 mol), prepared according to the procedure of Example 1, Part D, in hexane (40 mL) was added, dropwise, a solution of 2,4-dimethoxyphenylisocyanate (0.358 g, 0.002 mol) in hexane (20 mL) and the reaction mixture

was stirred at ambient temperature for 4.5 hours. The reaction mixture was concentrated under vacuum and the residue was chromatographed with 7:3 hexane-ethyl acetate. The resulting solid was triturated with hexane to give the title compound (0.83 g, 0.0014 mol) as a glassy solid. ^{1}H NMR ($CDCl_3$) δ 7.7-7.1(m,10H), 6.8-6.1(m,3H), 3.8(s,3H), 3.7(s,3H), 3.45(s,1H), 3.4-3.3(m,2H), 3.2(t,2H,J = 7Hz), 3.0(t,2H,J = 7Hz), 1.8-1.1-(m,16H), 0.9(t,3H,J = 8Hz).

EXAMPLE 6

Preparation of N'-(2,4-difluorophenyl)-N-heptyl-N-[5-(1-methyl-4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]urea

To a solution of potassium carbonate (0.056 g, 0.00042 mol) in dry tetrahydrofuran (10 mL) was added, portionwise as a solid, N'-(2,4-difluorophenyl)-N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptylurea (0.25 g, 0.00042 mol) and the reaction mixture was stirred at ambient temperature for 10 minutes. To this reaction mixture was added, dropwise, methyl iodide (0.039 mL, 0.0895 g, 0.00063 mol) and the reaction mixture was stirred for 18 hours at ambient temperature. The reaction mixture was then treated with N,N-dimethylformamide (1.0 mL) and methyl iodide (0.1 mL) and the reaction mixture was stirred at reflux for an additional 24 hours. The reaction mixture was cooled, poured into water and extracted with ethyl acetate. The combined organic extracts were dried over magnesium sulfate and concentrated under vacuum. The residue was chromatographed with 3:7 hexane-ethyl acetate to give the title compound (0.13 g, 0.00022 mol) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 8.1-8.0(m,1H), 7.5-7.1(m,10H), 6.9-6.7(m,2H), 6.4(s,1H), 3.5(s,3H), 3.4-3.2(m,5H), 1.9-1.2(m,17H), 0.9(t,3H,J = 8Hz).

EXAMPLE 7

Preparation of N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptyl-N'-methylurea

To a solution of N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-1-heptanamine (0.30 g, 0.0007 mol) in hexane (15 mL) was added methylisocyanate (0.06 mL, 0.057 g, 0.001 mol) and the reaction mixture was stirred at ambient temperature for 18 hours. The reaction mixture was concentrated under vacuum and the residue was chromatographed with 1:1 hexane-ethyl acetate. The resulting oil was triturated with hexane to give the title compound (0.23 g, 0.00047 mol) as a white solid, mp 93-96°. ^{1}H NMR ($CDCl_3$) δ 7.6-7.2-(m,11H), 4.35-2.7(m,9H), 1.9-1.2(m,16H), 0.9(t,3H,J = 8Hz).

EXAMPLE 8

Preparation of N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptyl-N'-propylurea

To a solution of N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-1-heptanamine (0.36 g, 0.0008 mol) in hexane (15 mL) was added propylisocyanate (0.094 mL, 0.085 g, 0.001 mol), and the reaction mixture was stirred at ambient temperature for 4 hours. The reaction mixture was then treated with additional propylisocyanate (0.094 mL, 0.085 g, 0.001 mol) and stirred at ambient temperature overnight and then at reflux for 72 hours. The reaction mixture was concentrated under vacuum and the residue was chromatographed using 2:8 hexane-ethyl acetate. The resulting oil was triturated with hexane to give the title compound (0.8 g, 0.00015 mol) as a white solid, mp 78-80°. ^{1}H NMR ($CDCl_3$) δ 7.6-7.2(m,10H), 4.4-(t,1H,J = 7Hz), 3.4-2.9(m,8H), 1.9-1.1(m,19H), 1.0-0.75(m,6H).

EXAMPLE 9

Preparation of N'-(2,4-difluorophenyl)-N-[2-(4,5-diphenyl-1H-imidazol-2-ylthio)ethyl]-N-propylurea

Part A. To a solution of bromoacetylchloride (25.51 mL, 48.67 g, 0.31 mol) in methylene chloride (200 mL) at -15° was added, dropwise, a solution of propylamine (24,62 mL, 17.7 g, 0.3 mol) in methylene chloride (100 mL) and the reaction mixture was stirred at 0° for 30 minutes and then stirred at ambient temperature for 30 minutes. The reaction mixture was poured into water and then extracted with methylene chloride. The combined organic extracts were dried over magnesium sulfate and concentrated under vacuum. The residue was distilled to give bromo-N-propylacetamide as a clear liquid, bp 138-142°. ^{1}H NMR ($CDCl_3$) δ 7.1(s,1H), 3.9(d,2H,J = 6Hz), 3.3(m,2H), 1.6(m,2H), 0.9(t,3H,J = 7Hz).

Part B. A portion of sodium hydride, 60% in mineral oil (0.4 g, 0.01 mol), was washed twice with hexane (10 mL) and then the hexane was replaced with N,N-dimethylformamide (100 mL). To this solution was added, portionwise as a solid, sodium iodide (0.4 g, 0.003 mol) and then, dropwise, a solution of diphenylimidazole (2.52 g, 0.01 mol) in N,N-dimethylformamide (10 mL) followed by the dropwise addition of a solution of bromo-N-propylacetamide (1.80 g, 0.01 mol) in N,N-dimethylformamide (10 mL). The reaction mixture was stirred at reflux for 18 hours, then cooled and poured, carefully, into ice water, and then extracted with ethyl acetate. The combined organic extracts were backwashed with brine, dried over magnesium sulfate and concentrated under vacuum. The residue was chromatographed using 1:1 hexane-ethyl acetate and the resulting solid was recrystallized from acetonitrile to give 2-(4,5-diphenyl-1H-imidazol-2-ylthio)-N-propylacetamide as a white solid, mp 183-185°. ^{1}H NMR (DMSO-d_6) δ 12.6-(s,1H), 8.3(s,1H), 7.5-7.1(m,10H), 3.8(s,2H), 3.0(q,2H,J = 7.5Hz), 1.4(sextet, 2H,J = 9Hz), 0.8(t,3H,J = 6Hz).

Part C. Employing the method of Example 1, Part D, but using 2-(4,5-diphenyl-1H-imidazol-2-ylthio)-N-propylacetamide, N-[2-(4,5-diphenyl-1H-imidazol-2-ylthio)ethyl]-1-propanamine (0.28 g, 0.00083 mol) was obtained as an oil. ^{1}H NMR ($CDCl_3$) δ 7.9-7.6(m,2H), 7.5-7.1(m,10H), 3.1(s,4H), 2.6(t,2H,J = 6Hz), 1.4-(sextet, 2H,J = 12Hz), 0.8(t,3H,J = 9Hz).

Part D. Employing the method of Example 1, Part E, but using N-[2-(4,5-diphenyl-1H-imidazol-2-ylthio)-ethyl]-1-propanamine, the title compound (0.20 g, 0.00045 mol) was obtained as a white solid, mp 189-190°. ^{1}H NMR ($CDCl_3$) δ 11.6-11.2(s,1H), 7.8-7.6(s,1H), 7.6-6.9(m,10H), 6.8-6.6(m,2H), 3.8(t,2H,J = 7Hz), 3.4(t,2H,J = 6.5Hz), 3.2(t,2H,J = 6Hz), 1.8-1.6(m,4H), 1.0(t,3H,J = 7.5Hz).

EXAMPLE 118

Preparation of N-[5-(4,5-bis(4-methoxyphenyl)-1H-imidazol-2-ylthio]-pentyl]-N'-(2,4-difluorophenyl)-N-heptylurea

Part A. A solution of γ-valerolactone (25.0 g, 0.249 mol) in toluene (50 mL) and n-heptylamine (35.96 g, 0.312 mol) was heated to reflux for 18 hours under a nitrogen atmosphere. The reaction mixture was allowed to cool to ambient temperature, diluted with ethyl acetate (300 mL), washed with 1 N aqueous HCl (50 mL), water, brine, dried over magnesium sulfate and concentrated to give a white solid. The product was crystallized from ethyl ether:hexane to give N-heptyl-5-hydroxypentanamide (41.8 g, 0.194 mol) as white plates, mp 55-6°. ^{1}H NMR ($CDCl_3$) δ 6.06(bs,1H), 3.61(t,2H), 3.24(q,2H), 3.19(bs,1H), 2.19-(t,2H), 1.80-1.23(m,14H), 0.866(t,3H).

Part B. To a solution of lithium aluminum hydride (6.7 g, 0.176 mol) in dry tetrahydrofuran (300 mL), a solution of N-heptyl-5-hydroxypentanamide (19.0 g, 0.088 mol) in dry tetrahydrofuran (100 mL) under a nitrogen atmosphere was added dropwise. The reaction mixture was heated to reflux for 18 hours, allowed to cool to room temperature and was poured slowly into a stirred mixture of 10% aqueous sodium sulfate (400 mL) and ice (200 mL). The resulting slurry was filtered through a bed of Celite® and the filtrate was extracted with ethyl acetate (2 x 500 mL). The combined organic layer was washed with water, brine, dried over magnesium sulfate and concentrated to give a viscous yellow oil. The product was crystallized from hexane to give N-(5-hydroxypentyl)-N-heptylamine (15.2 g, 0.075 mol) as a white powder, mp 47-8°. ^{1}H NMR ($CDCl_3$) δ 3.63(t,2H), 2.63(q,4H), 2.39(bs,2H), 1.66-1.24(m,16H), 0.905(t,3H).

Part C. To a solution of N-(5-hydroxypentyl)-N-heptylamine (11.65 g, 0.0578 mol) in methylene chloride (75 mL) under a nitrogen atmosphere cooled to 0°, 2,4-difluorophenylisocyanate (8.97 g, 0.0578 mol) was added slowly. The reaction mixture was stirred for 1 hour, poured into 1 N aqueous HCl (200 mL) and was extracted with ethyl acetate (300 mL). The combined organic layer was washed with water, brine, dried over magnesium sulfate and was concentrated to give N'-(2,4-difluorophenyl)-N-heptyl-N-5-hydroxypentylurea as a pale yellow oil (20.0 g, 0.056 mol). ^{1}H NMR ($CDCl_3$) δ 8.03 (m,1H), 6.88-6.59-(m,2H), 6.45(bs,1H), 3.68(t,2H), 3.33(m,4H), 1.81-1.22(m,16H), 0.907(t,3H).

Part D. To a solution of N'-(2,4-difluorophenyl)-N-heptyl-N-5-hydroxypentylurea (15.0 g, 0.042 mol) and carbon tetrabromide (16.75 g, 0.051 mol) in methylene chloride (350 mL) under a nitrogen atmosphere at ambient temperature, a solution of triphenylphosphine (13.24 g, 0.051 mol) in methylene chloride (100 mL) was added slowly. The reaction mixture stirred for 3 hours and was concentrated in vacuo to give crude viscous oil. The product was purified by flash chromatography on silica gel (400 mL) eluting with hexane:ethyl acetate (90:10 v:v) to give N-(5-bromopentyl)-N'-(2,4-difluorophenyl)-N-heptylurea as a viscous colorless oil (17.5 g, 0.042 mol). ^{1}H NMR ($CDCl_3$) δ 8.14-8.00(m,1H), 6.92-6.79(m,2H), 6.35-(bs,1H), 3.49-3.25(m,6H), 1.99-1.26(m,16H), 0.915(t,3H).

Part E. To a suspension of sodium hydride (0.88 g, 60% mineral oil dispersion, 0.0022 mol) (washed free of mineral oil with hexane) in N,N-dimethylformamide (15 mL) under a nitrogen atmosphere, cooled to

0°, a solution of 4,5-[bis-(4-methoxyphenyl)-1H-imidazol]-2-thione (0.63 g, 0.002 mol) in N,N-dimethylformamide (5 mL) was added slowly. The reaction mixture was stirred for 2 hours and then a solution of N-(5-bromopentyl)-N'-(2,4-difluorophenyl)-N-heptylurea (0.845 g, 0.002 mol) in N,N-dimethylformamide (3 mL) was added. The reaction mixture was allowed to warm to ambient temperature, stirred an additional 2 hours, poured into water (50 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with water, brine, dried over magnesium sulfate and concentrated to give a viscous oil. The product was purified by flash chromatography on silica gel (100 mL) eluting with hexane:ethyl acetate (70:30 v:v) to give the title compound as a pure yellow foam (0.98 g, 0.0015 mol). ^{1}H NMR ($CDCl_3$) δ 10.15(bs,1H), 7.87-7.76(m,1H), 7.51(d,2H), 7.3(d,2H), 6.86-6.6(m,6H), 6.42(d,1H), 3.8(s, 6H), 3.4(t,2H), 3.26(t,2H), 2.99(t,2H), 1.84-1.25(m,16H), 0.89(t,3H).

EXAMPLE 191

Preparation of N-(2,4-difluorophenyl)-N'-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]urea

Part A. A mixture of 5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentanoic acid (4.0 g, 0.011 mol) and urea (1.36 g, 0.023 mol) was heated to 179-180° for 5 hours. The cooled reaction mixture was partitioned in sodium carbonate (5%) and extracted with chloroform. The organic layers were washed with saturated sodium chloride solution then dried over magnesium sulfate and concentrated under vacuum. The residue was chromatographed with 9:1 ethyl acetate-methanol to give 5-(4,5-diphenyl-1H-imidazol-2-ylthio)-pentanamide (0.73 g, 0.002 mol) as a white solid, mp 136-138°. ^{1}H NMR ($CDCl_3$) δ 10.65(s,1H), 7.7-7.2-(m,10H), 5.9(s,1H), 5.4(s,1H), 3.0(t,2H,J = 7.4Hz), 2.3(t,2H,J = 8Hz), 2.0-1.6(m,4H).

Part B. Employing the method of Example 1, Part D, using 5-(4,5-diphenyl-1H-imidazol-2-ylthio)-pentanamide (2.0 g, 0.0057 mol), 5-(4,5-diphenyl-1H-imidazol-2-ylthio)-1-pentanamine (0.32 g, 0.00095 mol) was obtained as a tan solid, mp 111-113°. ^{1}H NMR (DMSO-d_6) δ 7.5-7.2(m,12H), 3.1-(t,2H,J = 7.2Hz), 2.5(t,2H,J = 6.2Hz), 1.8-1.3(m,7H).

Part C. A solution of 5-(4,5-diphenyl-1H-imidazol-2-ylthio)-1-pentanamine (0.34 g, 0.001 mol) and 2,4-difluorophenyliso cyanate (0.24 mL, 0.31 g, 0.002 mol) in toluene (10 mL) was stirred at ambient temperature for 120 hours. The solution was concentrated under vacuum to give a residue (0.53 g) which was chromatographed with 1:1 hexane-ethyl acetate. The resulting solid was triturated with cold acetonitrile to give the title compound (0.13 g, 0.0026 mol) as a white solid, mp 187-198°. ^{1}H NMR (DMSO-d_6) δ 12.5(s,1H), 8.2-8.0(m,2H), 7.5-7.1(m,11H), 7.0-6.9(m,1H), 6.6-6.5(m,1H), 3.2-3.0(m,4H), 1.8-1.3(m,6H).

EXAMPLE 207

Preparation of N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N'-octyl-N-phenylurea

To a solution of N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]benzeneamine (0.41 g, 0.001 mol) in toluene (25 mL) was added n-octylisocyanate (0.23 g, 0.0015 mol). The reaction mixture was stirred at reflux for 18 hours and then the solvent was removed under vacuum. The residue (1.0 g) was chromatographed with 7:3 hexane-ethyl acetate. The resulting solid was triturated with hexane to give the title compound (0.32 g, 0.00056 mol) as a white solid, mp 74-76°. ^{1}H NMR ($CDCl_3$) δ 11.8(s,1H), 7.75-7.1-(m,15H), 4.3(t,1H,J = 6.0Hz), 3.8(t,2H,J = 7.0Hz), 3.0(quintet,4H,J = 6.0Hz), 1.9-0.90(m,18H), 0.8-(t,3H,J = 7.0Hz).

EXAMPLE 209

Preparation of N-[5-[4,5-bis(4-hydroxyphenyl)-1H-imidazol-2-ylthio]pentyl]-N'-(2,4-difluorophenyl)-N-heptylurea

To a stirred solution of N-[5-[4,5-bis(4-methoxyphenyl)-1H-imidazol-2-ylthio]pentyl]-N'-(2,4-difluorophenyl)-N-heptylurea (0.78 g, 0.0012 mol) in methylene chloride (30 mL) cooled to -78° under a nitrogen atmosphere, 1M boron tribromide in methylene chloride (3.6 mL) was added. The reaction mixture stirred for 1 hour at 0°, was poured over ice (100 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layer was washed with 10% aqueous $NaHCO_3$ (50 mL), water, brine, dried over magnesium sulfate, and concentrated in vacuo to give the crude oil. The product was purified by flash chromatography on silica gel (100 mL) eluting with hexane:ethyl acetate (40:60 v:v) to give a white foam,

mp 110-12° (0.5 g, 0.00008 mol). ^{1}H NMR (DMSO-d_6) δ 12.22 (bs,1H), 9.55(bs,1H), 9.32(bs,1H),7.92(s,1H), 7.45-6.6(m,11H), 3.24(m,4H), 3.06(t,2H), 1.77-1.17(m,16H), 0.88(t,3H).

EXAMPLE 211

Preparation of N-[5-(1H,9H-dibenz-[4,5:8,9][1,3]dioxonino-[6,7-d]imidazol-2-ylthio)pentyl]-N'-(2,4-difluorophenyl)-N-heptylurea

Part A. To a suspension of sodium hydride (washed free of mineral oil with hexane) (2.45 g, 80% oil dispersion, 0.081 mol) in dry N,N-dimethylformamide (50 mL) under a nitrogen atmosphere, cooled to 0°, a solution of salisaldehyde (10.0 g, 81.9 mmol) in dry N,N-dimethylformamide (10 mL) was added slowly. The reaction mixture was stirred at 0° for 2 hours and diiodomethane (11.3 g, 0.041 mol) was added. The reaction mixture was allowed to warm to ambient temperature for 18 hours and then was warmed to 60° for 20 hours. The reaction was allowed to cool to ambient temperature, poured into 1 N aqueous HCl (100 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic extract was washed with water, brine, dried over magnesium sulfate and concentrated to give a solid. The product was purified by flash chromatography on silica gel (300 mL) eluting with methylene chloride (100%) to give 2,2'-(methylenedioxy)-bis-(2-benzaldehyde) as a white crystalline solid, mp 131 to 3° (5.1 g, 0.0199 mol). ^{1}H NMR ($CDCl_3$) δ 10.47(s, 2H), 7.87(d,2H), 7.68-7.54(m,2H), 7.21(d,2H), 7.15(t,2H), 6.02(s, 2H).

Part B. A mixture of 2,2'-(methylenedioxy)-bis-(2-benzaldehyde) (5.0 g, 0.0195 mol), potassium cyanide (0.63 g, 0.0975 mol) in ethanol (75 mL) and water (50 mL) was heated to reflux for 6 hours. The reaction mixture was allowed to cool to ambient temperature, was concentrated in vacuo and the resultant aqueous residue was partitioned between ethyl acetate and water. The organic layer was washed with water, brine, dried over magnesium sulfate and concentrated to give a viscous oil. The product was purified by flash chromatography on silica gel (250 mL) eluting with hexane:ethyl acetate (80:20 v:v) to give 13-hydroxy-dibenzo[d,h][1,3]-dioxonino-12(13H)-one as a crystalline solid, mp 129-30° (2.5 g, 0.0975 mol). ^{1}H NMR (DMSO-d_6) δ 7.49(t,2H), 7.29-7.08(m,6H), 6.40(d,1H), 5.97(d,1H), 5.92(d,1H), 5.24-(d,1H).

Part C. A solution of 13-hydroxy-dibenzo[d,h][1,3]-dioxonino-12(13H)-one (2.0 g, 0.0078 mol), thiourea (0.82 g, 0.0108 mol) and hexanol (25 mL), equipped with a column of 4° A sieves and a condenser, was heated to 160° for 20 hours under a nitrogen atmosphere. The reaction mixture was allowed to cool to ambient temperature and was diluted with ethyl ether (100 mL) to give a solid. The solid was washed with ethyl ether and dried to give N-(1H,9H-dibenz-[4,5:8,9][1,3]dioxonino-[6,7-d]imidazol)-2-thione as a white crystalline powder (1.6 g, 0.00539 mol), mp >250°. ^{1}H NMR (DMSO-d_6) δ 12.5(s,2H), 7.43-7.08-(m,8H), 6.2-5.0(bd,2H).

Part D. Employing the method of Example 118, Part E, but using N-(1H,9H-dibenz-[4,5:8,9][1,3]-dioxonino-[6,7-d]imidazol)-2-thione, the title compound was isolated as a white foam, mp 65-70° (0.85 g, 0.00134 mol). ^{1}H NMR ($CDCl_3$) δ 10.35-10.10(bs,1H), 7.56(m,1H), 7.30-6.95(m,10H), 6.4(d,1H), 5.70-5.20-(bs,2H), 3.40-3.19(m,4H), 3.08(t,2H), 1.85-1.23(m,16H), 0.88(t,3H).

EXAMPLE 212

Preparation of N'-[5-(1H-dibenz[2,3:6,7]oxedino[4,5-d]imidazol-2-ylthio)pentyl]-N-(2,4-difluorophenyl)-N-heptylurea

Employing the method of Example 118, Part E, but using 1H-dibenz[2,3:6,7]oxedino[4,5-d]imidazol)-2-thione, the title compound was isolated as a white powder, mp 82-7° (0.36 g, 0.00059 mol). ^{1}H NMR ($CDCl_3$) δ 9.75-8.5(bs, 2H), 7.84-7.59(m,3H), 7.43-7.05(m,6H), 5.13-6.53(m,3H), 3.43-3.13(m,6H), 1.75-1.20-(m,16H). 0.88(t,3H).

Additional ureas, which are listed in Tables 1 and 2, were prepared or could be prepared analogously according to the procedures listed above.

Table 1

Ex. No.	R^1	R^2	R^3	R^4	n	R^6	mp°C
1	C_6H_5	C_6H_5	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	96-98
2	C_6H_5	C_6H_5	H	C_6H_5	5	$(CH_2)_6CH_3$	amorphous solid
3	C_6H_5	C_6H_5	H	2,4-diFC_6H_3	8	$(CH_2)_6CH_3$	89-91
4	C_6H_5	C_6H_5	H	2,4-diFC_6H_3	8	$(CH_2)_3CH_3$	114-115
5	C_6H_5	C_6H_5	H	2,4-di$CH_3OC_6H_3$	5	$(CH_2)_6CH_3$	glassy solid
6	C_6H_5	C_6H_5	CH_3	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	oil
7	C_6H_5	C_6H_5	H	CH_3	5	$(CH_2)_6CH_3$	93-96
8	C_6H_5	C_6H_5	H	n-C_3H_7	5	$(CH_2)_6CH_3$	78-80
9	C_6H_5	C_6H_5	H	2,4-diFC_6H_3	2	$(CH_2)_2CH_3$	189-190
10	C_6H_5	C_6H_5	H	2,4-diFC_6H_3	10	$(CH_2)_3CH_3$	
11	C_6H_5	C_6H_5	H	2,4-diFC_6H_3	5	CH_2CH_3	
12	C_6H_5	C_6H_5	H	2,4-diFC_6H_3	3	$(CH_2)_8CH_3$	

Table 1 (continued)

Ex. No.	R^1	R^2	R^3	R^4	n	R^6	mp°C
13	C_6H_5	C_6H_5	H	2,4-diFC_6H_3	3	$(CH_2)_{10}CH_3$	
14	C_6H_5	C_6H_5	H	2,4-diFC_6H_3	10	$(CH_2)_{10}CH_3$	
15	C_6H_5	C_6H_5	CH_3	2,4-diFC_6H_3	8	$(CH_2)_3CH_3$	
16	C_6H_5	C_6H_5	$n\text{-}C_3H_7$	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	
17	C_6H_5	C_6H_5	$n\text{-}C_6H_{13}$	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	
18	C_6H_5	C_6H_5	$CH_2CH{=}CH_2$	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	
19	C_6H_5	C_6H_5	$CH_2C_6H_5$	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	
20	C_6H_5	C_6H_5	C_6H_5	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	99-101
21	C_6H_5	C_6H_5	C_6H_5	2,4-diFC_6H_3	8	$(CH_2)_3CH_3$	
22	C_6H_5	C_6H_5	4-FC_6H_4	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	
23	C_6H_5	C_6H_5	4-$CH_3C_6H_4$	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	
24	C_6H_5	C_6H_5	4-$CH_3OC_6H_4$	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	
25	C_6H_5	C_6H_5	4-$CF_3C_6H_4$	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	
26	C_6H_5	C_6H_5	4-ClC_6H_4	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	
27	C_6H_5	C_6H_5	3-FC_6H_4	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	
28	C_6H_5	C_6H_5	2-FC_6H_4	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	
29	C_6H_5	C_6H_5	3-$CH_3OC_6H_4$	3-FC_6H_4	5	$(CH_2)_6CH_3$	
30	C_6H_5	C_6H_5	3-$CH_3OC_6H_4$	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	
31	C_6H_5	C_6H_5	2-$CF_3C_6H_4$	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	
32	C_6H_5	C_6H_5	4-FC_6H_4	2,4-diFC_6H_3	8	$(CH_2)_3CH_3$	

Table 1 (continued)

Ex. No.	R^1	R^2	R^3	R^4	n	R^6	mp°C
33	C_6H_5	C_6H_5	2-FC_6H_4	2,4-diFC_6H_3	8	$(CH_2)_3CH_3$	
34	C_6H_5	C_6H_5	3-$CH_3OC_6H_4$	2,4-diFC_6H_3	8	$(CH_2)_3CH_3$	
35	C_6H_5	C_6H_5	4-$CH_3OC_6H_4$	2,4-diFC_6H_3	8	$(CH_2)_3CH_3$	
36	C_6H_5	C_6H_5	4-$CH_3OC_6H_4$	C_6H_5	5	$(CH_2)_5CH_3$	
37	C_6H_5	C_6H_5	H	2-$CF_3C_6H_4$	8	$(CH_2)_6CH_3$	
38	C_6H_5	C_6H_5	H	3-$CF_3C_6H_4$	5	$(CH_2)_6CH_3$	
39	C_6H_5	C_6H_5	H	4-$CF_3C_6H_4$	5	$(CH_2)_6CH_3$	
40	C_6H_5	C_6H_5	H	2-$CH_3C_6H_4$	5	$(CH_2)_6CH_3$	
41	C_6H_5	C_6H_5	H	3-$CH_3C_6H_4$	5	$(CH_2)_6CH_3$	
42	C_6H_5	C_6H_5	H	4-$CH_3C_6H_4$	5	$(CH_2)_6CH_3$	
43	C_6H_5	C_6H_5	H	3-$C_2H_5C_6H_4$	5	$(CH_2)_6CH_3$	
44	C_6H_5	C_6H_5	H	3-$(CH_3)_2CHC_6H_4$	5	$(CH_2)_6CH_3$	
45	C_6H_5	C_6H_5	H	2-BrC_6H_4	5	$(CH_2)_6CH_3$	
50	C_6H_5	C_6H_5	H	3-BrC_6H_4	5	$(CH_2)_6CH_3$	
51	C_6H_5	C_6H_5	H	4-BrC_6H_4	5	$(CH_2)_6CH_3$	
52	C_6H_5	C_6H_5	H	2-FC_6H_4	5	$(CH_2)_6CH_3$	
53	C_6H_5	C_6H_5	H	3-FC_6H_4	5	$(CH_2)_6CH_3$	124-126
54	C_6H_5	C_6H_5	H	4-FC_6H_4	5	$(CH_2)_6CH_3$	
55	C_6H_5	C_6H_5	H	3-ClC_6H_4	5	$(CH_2)_6CH_3$	
56	C_6H_5	C_6H_5	H	4-n-$C_4H_9C_6H_4$	5	$(CH_2)_6CH_3$	

Table 1 (continued)

Ex. No.	R1	R2	R3	R4	n	R6	mp°C
57	C_6H_5	C_6H_5	H	4-$CH_3OC_6H_4$	5	$(CH_2)_6CH_3$	
58	C_6H_5	C_6H_5	H	4-$CH_3CH_2O_2CC_6H_4$	5	$(CH_2)_6CH_3$	
59	C_6H_5	C_6H_5	H	2,3-di$CH_3C_6H_3$	5	$(CH_2)_6CH_3$	
60	C_6H_5	C_6H_5	H	2,5-di$CH_3C_6H_3$	5	$(CH_2)_6CH_3$	
61	C_6H_5	C_6H_5	H	2,6-di$CH_3C_6H_3$	5	$(CH_2)_6CH_3$	
62	C_6H_5	C_6H_5	H	2,4-di$CH_3C_6H_3$	5	$(CH_2)_6CH_3$	
63	C_6H_5	C_6H_5	H	2,3-diClC_6H_3	5	$(CH_2)_6CH_3$	
64	C_6H_5	C_6H_5	H	2,6-diClC_6H_3	5	$(CH_2)_6CH_3$	90-92
65	C_6H_5	C_6H_5	H	2,4-diClC_6H_3	5	$(CH_2)_6CH_3$	
66	C_6H_5	C_6H_5	H	2,5-diClC_6H_3	5	$(CH_2)_6CH_3$	
67	C_6H_5	C_6H_5	H	2,3-diFC_6H_3	5	$(CH_2)_6CH_3$	
68	C_6H_5	C_6H_5	H	2,5-diFC_6H_3	5	$(CH_2)_6CH_3$	
69	C_6H_5	C_6H_5	H	2,4,6-triClC_6H_2	5	$(CH_2)_6CH_3$	
70	C_6H_5	C_6H_5	H	2,4,5-triClC_6H_2	5	$(CH_2)_6CH_3$	
71	C_6H_5	C_6H_5	H	2,4,6-triFC_6H_2	5	$(CH_2)_6CH_3$	78-80
72	C_6H_5	C_6H_5	H	2,4,5-triFC_6H_2	5	$(CH_2)_6CH_3$	
73	C_6H_5	C_6H_5	H	3,4,5-tri$CH_3OC_6H_2$	5	$(CH_2)_6CH_3$	
74	C_6H_5	C_6H_5	H	2,4,6-tri$CH_3C_6H_2$	5	$(CH_2)_6CH_3$	
75	C_6H_5	C_6H_5	H	4-Cl,2-$CH_3C_6H_3$	5	$(CH_2)_6CH_3$	
76	C_6H_5	C_6H_5	H	4-Cl,2,5-di$CH_3C_6H_2$	5	$(CH_2)_6CH_3$	

Table 1 (continued)

Ex. No.	R^1	R^2	R^3	R^4	n	R^6	mp-°C
77	C_6H_5	C_6H_5	H	4-Cl,3-$CF_3C_6H_3$	5	$(CH_2)_6CH_3$	
78	C_6H_5	C_6H_5	H	4-Cl,2,6-di$CH_3C_6H_2$	5	$(CH_2)_6CH_3$	
79	C_6H_5	C_6H_5	H	3-Cl,4-$CH_3C_6H_3$	5	$(CH_2)_6CH_3$	
80	C_6H_5	C_6H_5	H	3-Cl,4-FC_6H_3	5	$(CH_2)_6CH_3$	
81	C_6H_5	C_6H_5	H	5-Cl,2-$CH_3OC_6H_3$	5	$(CH_2)_6CH_3$	
82	C_6H_5	C_6H_5	H	2-Cl,5-$CF_3C_6H_3$	5	$(CH_2)_6CH_3$	
83	C_6H_5	C_6H_5	H	4-F,2-$CH_3C_6H_3$	5	$(CH_2)_6CH_3$	
84	C_6H_5	C_6H_5	H	4-$NO_2C_6H_4$	5	$(CH_2)_6CH_3$	
85	C_6H_5	C_6H_5	H	4-CNC_6H_4	5	$(CH_2)_6CH_3$	68-70
86	C_6H_5	C_6H_5	H	4-$NH_2C_6H_4$	5	$(CH_2)_6CH_3$	
87	C_6H_5	C_6H_5	H	4-$CH_3NHC_6H_4$	5	$(CH_2)_6CH_3$	
88	C_6H_5	C_6H_5	H	4-$(CH_3)_2NC_6H_4$	5	$(CH_2)_6CH_3$	
89	C_6H_5	C_6H_5	H	4-HOC_6H_4	5	$(CH_2)_6CH_3$	
90	C_6H_5	C_6H_5	H	2-pyridinyl	5	$(CH_2)_6CH_3$	
91	C_6H_5	C_6H_5	H	3-pyridinyl	5	$(CH_2)_6CH_3$	
92	C_6H_5	C_6H_5	H	4-pyridinyl	5	$(CH_2)_6CH_3$	
93	C_6H_5	C_6H_5	H	2,6-pyrimidinyl	5	$(CH_2)_6CH_3$	
94	C_6H_5	C_6H_5	H	C_6H_{11}	5	$(CH_2)_6CH_3$	95-97
95	C_6H_5	C_6H_5	H	C_5H_9	5	$(CH_2)_6CH_3$	
96	C_6H_5	C_6H_5	H	n-C_6H_{13}	5	$(CH_2)_6CH_3$	

Table 1 (continued)

Ex. No.	R^1	R^2	R^3	R^4	n	R^6	mp°C
97	C_6H_5	C_6H_5	H	n-C_8H_{17}	5	$(CH_2)_6CH_3$	oil(a)
98	C_6H_5	C_6H_5	H	n-C_3H_7	5	$(CH_2)_6CH_3$	
99	C_6H_5	C_6H_5	H	CF_3	5	$(CH_2)_6CH_3$	
100	C_6H_5	C_6H_5	H	$CH_2CH=CHCH_3$	5	$(CH_2)_6CH_3$	
101	C_6H_5	C_6H_5	H	$CH_2CH=CH_2$	5	$(CH_2)_6CH_3$	
102	C_6H_5	C_6H_5	H	$CH_2CH=CHCH_2CH_3$	5	$(CH_2)_6CH_3$	
103	C_6H_5	C_6H_5	H	$CH_2C\equiv CCH_3$	5	$(CH_2)_6CH_3$	
104	C_6H_5	C_6H_5	H	n-C_4H_9	5	$(CH_2)_6CH_3$	
105	C_6H_5	C_6H_5	H	$CH(CH_3)_2$	5	$(CH_2)_6CH_3$	84-86
106	C_6H_5	C_6H_5	H	CF_2CF_3	5	$(CH_2)_6CH_3$	
107	2-pyridinyl	2-pyridinyl	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	oil(b)
108	3-pyridinyl	3-pyridinyl	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	
109	4-pyridinyl	4-pyridinyl	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	
110	2-thienyl	2-thienyl	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	75-80
111	$C_6H_5CH_2$	$C_6H_5CH_2$	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	
112	$C_6H_5(CH_2)_2$	$C_6H_5(CH_2)_2$	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	
113	$C_6H_5(CH_2)_5$	$C_6H_5(CH_2)_5$	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	
114	4-FC_6H_4	4-FC_6H_4	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	82-84
115	4-FC_6H_4	4-FC_6H_4	H	2,4-diFC_6H_3	8	$(CH_2)_6CH_3$	
116	4-FC_6H_4	4-FC_6H_4	H	n-C_3H_7	8	$(CH_2)_6CH_3$	

Table 1 (continued)

Ex. No.	R^1	R^2	R^3	R^4	n	R^6	mp°C
117	4-FC_6H_4	4-FC_6H_4	H	2,4,6-triFC_6H_2	5	$(CH_2)_6CH_3$	
118	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	55-59
119	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	2,4-diFC_6H_3	8	$(CH_2)_6CH_3$	
120	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	n-C_3H_7	8	$(CH_2)_6CH_3$	
121	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	2,4,6-triFC_6H_2	5	$(CH_2)_6CH_3$	
122	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	63-65(c)
123	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	H	2,4-diFC_6H_3	8	$(CH_2)_6CH_3$	
124	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	H	n-C_3H_7	8	$(CH_2)_6CH_3$	
125	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	H	2,4,6-triFC_6H_2	5	$(CH_2)_6CH_3$	
126	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NHC_6H_4$	H	CH_3	8	$(CH_2)_6CH_3$	
127	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	
128	C_6H_5	4-$CH_3SC_6H_4$	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	
129	C_6H_5	4-$CH_3SOC_6H_4$	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	
130	C_6H_5	4-$CH_3SO_2C_6H_4$	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	
131	4-ClC_6H_4	4-ClC_6H_4	H	2,4-di$CH_3OC_6H_3$	5	$(CH_2)_6CH_3$	
132	4-BrC_6H_4	4-BrC_6H_4	H	2,4-di$CH_3C_6H_3$	8	$(CH_2)_6CH_3$	
133	C_6H_5	4-FC_6H_4	H	2,4,6-triFC_6H_2	8	$(CH_2)_6CH_3$	
134	4-$CF_3C_6H_4$	4-$CF_3C_6H_4$	H	4-FC_6H_4	5	$(CH_2)_6CH_3$	
135	2-ClC_6H_4	2-ClC_6H_4	H	2,4,6-triFC_6H_2	4	$(CH_2)_7CH_3$	
136	3-ClC_6H_4	3-ClC_6H_4	H	2,4-di$CH_3OC_6H_3$	6	$(CH_2)_8CH_3$	

Table 1 (continued)

Ex. No.	R^1	R^2	R^3	R^4	n	R^6	mp°C
137	4-ClC_6H_4	4-ClC_6H_4	H	2,4-$diFC_6H_3$	5	$(CH_2)_6CH_3$	55-57(d)
138	4-FC_6H_4	3-ClC_6H_4	H	2,4-$diFC_6H_3$	5	$(CH_2)_6CH_3$	
139	4-$nC_4H_9OC_6H_4$	4-$nC_4H_9OC_6H_4$	H	C_6H_5	5	$(CH_2)_6CH_3$	
140	3,4-$diClC_6H_3$	C_6H_5	H	n-C_3H_7	6	$(CH_2)_6CH_3$	
141	C_6H_5	3-pyridinyl	H	C_6H_{11}	5	$(CH_2)_6CH_3$	
142	C_6H_5	3-pyridinyl	H	2,4-$diFC_6H_3$	5	$(CH_2)_6CH_3$	
143	C_6H_5	3-pyridinyl	H	2,4-$diFC_6H_3$	8	$(CH_2)_6CH_3$	
144	C_6H_5	3-pyridinyl	H	n-C_3H_7	8	$(CH_2)_6CH_3$	
145	4-FC_6H_4	3-pyridinyl	H	2,4,6-$triFC_6H_2$	5	$(CH_2)_6CH_3$	
146	4-$CH_3OC_6H_4$	3-pyridinyl	H	2,4,6-$triFC_6H_2$	6	$(CH_2)_6CH_3$	
147	C_6H_5	2-thienyl	H	2,4-$diFC_6H_3$	4	$(CH_2)_7CH_3$	
148	4-FC_6H_4	2-thienyl	H	C_6H_5	5	$(CH_2)_6CH_3$	
149	4-$CH_3OC_6H_4$	2-thienyl	H	2,4-$diCH_3OC_6H_3$	5	$(CH_2)_6CH_3$	
150	C_6H_5	4-pyridinyl	H	2,4-$diFC_6H_3$	5	$(CH_2)_6CH_3$	
151	4-FC_6H_4	4-pyridinyl	H	C_6H_5	5	$(CH_2)_6CH_3$	
152	4-$CH_3OC_6H_4$	4-pyridinyl	H	2,4-$diCH_3C_6H_3$	6	$(CH_2)_7CH_3$	
153	C_6H_5	2-pyridinyl	H	2,4-$diFC_6H_3$	5	$(CH_2)_6CH_3$	
154	3-F,4-ClC_6H_3	C_6H_5	H	2,4-$diFC_6H_3$	5	$(CH_2)_6CH_3$	
155	4-$CH_3OC_6H_4$	4-FC_6H_4	H	C_6H_5	8	$(CH_2)_6CH_3$	
156	4-FC_6H_4	C_6H_5	H	2,4-$diFC_6H_3$	5	$(CH_2)_6CH_3$	

Table 1 (continued)

Ex. No.	R^1	R^2	R^3	R^4	n	R^6	mp°C
157	4-BrC_6H_4	C_6H_5	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	
158	4-$CH_3OC_6H_4$	C_6H_5	H	2,4-di$CH_3OC_6H_3$	8	$(CH_2)_6CH_3$	
159	3,4-di$CH_3OC_6H_3$	3,4-di$CH_3OC_6H_3$	H	C_6H_5	9	$(CH_2)_5CH_3$	
160	C_6H_5	H	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	oil(e)
161	C_6H_5	H	H	2,4-di$CH_3OC_6H_3$	5	$(CH_2)_6CH_3$	
162	C_6H_5	H	H	2,4-diFC_6H_3	8	$(CH_2)_6CH_3$	
163	C_6H_5	H	H	n-C_3H_7	5	$(CH_2)_6CH_3$	
164	4-FC_6H_4	H	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	
165	4-$CH_3OC_6H_4$	H	H	2,4-diFC_6H_3	8	$(CH_2)_6CH_3$	
166	C_6H_5	H	H	C_6H_5	8	$(CH_2)_6CH_3$	
167	C_6H_5	CH_3	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	
168	C_6H_5	CH_3	H	2,4-diFC_6H_3	8	$(CH_2)_6CH_3$	
169	C_6H_5	CH_3	H	n-C_3H_7	8	$(CH_2)_6CH_3$	
170	C_6H_5	CH_3	H	2,4-di$CH_3OC_6H_3$	8	$(CH_2)_6CH_3$	
171	4-FC_6H_4	CH_3	H	2,5-diClC_6H_3	5	$(CH_2)_6CH_3$	
172	C_6H_5	n-C_4H_9	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	
173	C_6H_5	n-C_4H_9	H	2,4-diFC_6H_3	8	$(CH_2)_6CH_3$	
174	C_6H_5	n-C_4H_9	H	2,4-di$CH_3OC_6H_3$	5	$(CH_2)_6CH_3$	
175	C_6H_5	n-C_4H_9	H	n-C_3H_7	7	$(CH_2)_6CH_3$	
176	C_6H_5	n-C_8H_{17}	H	n-C_3H_7	9	$(CH_2)_5CH_3$	

Table 1 (continued)

Ex. No.	R^1	R^2	R^3	R^4	n	R^6	mp°C
177	C_6H_5	n-C_8H_{17}	H	2,4-diClC_6H_3	4	$(CH_2)_7CH_3$	
178	C_6H_5	C_5H_9	H	2,4-diFC_6H_3	8	$(CH_2)_6CH_3$	
179	C_6H_5	C_5H_9	H	2,4,5-triClC_6H_2	5	$(CH_2)_6CH_3$	
180	4-$CH_3OC_6H_4$	C_6H_{11}	H	C_6H_5	5	$(CH_2)_8CH_3$	
181	C_6H_5	C_6H_{11}-CH_2	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	
182	C_6H_5	C_6H_{11}-$(CH_2)_2$	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	
183	CH_3	CH_3	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	
184	CH_3	CH_3	H	n-C_3H_7	8	$(CH_2)_6CH_3$	
185	n-C_4H_9	n-C_4H_9	H	2,4,6-triFC_6H_2	8	$(CH_2)_6CH_3$	
186	H	H	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	oil(f)
187	H	H	H	2,4-diFC_6H_3	8	$(CH_2)_6CH_3$	
188	$(CH_3)_2CH$	$(CH_3)_2CH$	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	91-93
189	C_6H_5	C_6H_5	H	2,4-diFC_6H_3	2	$(CH_2)_6CH_3$	144-146
190	C_6H_5	C_6H_5	H	2,4-diFC_6H_3	5	$(CH_2)_2CH_3$	68-70
191	C_6H_5	C_6H_5	H	2,4-diFC_6H_3	5	H	187-189
192	C_6H_5	C_6H_5	H	$(C_6H_4)(C_6H_5)$	5	$(CH_2)_6CH_3$	119-121
193	$CH_3CH_2CH_2$	$CH_3CH_2CH_2$	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	78-80
194	2-pyridinyl	2-pyridinyl	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	80-83 (HCl salt)
195	3-$CH_3OC_6H_4$	3-$CH_3OC_6H_4$	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	100-102
196	2-$CH_3OC_6H_4$	2-$CH_3OC_6H_4$	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	(g)

Table 1 (continued)

Ex. No.	R^1	R^2	R^3	R^4	n	R^6	mp°C
197	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	68-70(h)
198	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	142-145 (HCl salt)
199	C_6H_{11}	C_6H_{11}	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	55-58(i)
200	C_6H_5	4-$(CH_3)_2NC_6H_4$	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	oil(j)
201	2-furanyl	2-furanyl	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	liq(k)
202	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	$CH_2(CH_3)_2$	5	$(CH_2)_6CH_3$	oil(l)
203	4-(t-C_4H_9)C_6H_4	4-(t-C_4H_9)C_6H_4	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	78-80(m)
204	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	2,4-diFC_6H_3	5	CH_3	65-75(n)
205	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	$CH(CH_3)_2$	5	$(CH_2)_6CH_3$	70-72(o)
206	C_6H_5	C_6H_5	H	$(CH_2)_7CH_3$	5	2,4,6-triFC_6H_2	oil(p)
207	C_6H_5	C_6H_5	H	$(CH_2)_7CH_3$	5	C_6H_5	74-76
208	C_6H_5	C_6H_5	H	$(CH_2)_7CH_3$	5	2,4,6-triFC_6H_2	99-101
209	4-HOC_6H_4	4-HOC_6H_4	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	110-112
210	$(CH_3)_2CH$	$(CH_3)_2CH$	H	$CH(CH_3)_2$	5	$(CH_2)_6CH_3$	oil(q)
211	C_6H_4-2-OCH_2O-2'-C_6H_4		H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	65-70
212		$C_6H_4OC_6H_4$	H	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	82-87
213	n-C_3H_7	n-C_3H_7	H	n-C_3H_7	5	$(CH_2)_6CH_3$	
214	2-pyridinyl	2-pyridinyl	H	C_6H_{11}	5	$(CH_2)_6CH_3$	
215	3-pyridinyl	3-pyridinyl	H	2,4-di$CH_3OC_6H_3$	5	$(CH_2)_6CH_3$	
216	4-pyridinyl	4-pyridinyl	H	2,4,6-triFC_6H_2	5	$(CH_2)_6CH_3$	

Table 1 (continued)

Ex. No.	R^1	R^2	R^3	R^4	n	R^6	mp°C
217	2-CH_3O-C_6H_4	2-CH_3O-C_6H_4	H	3-F-C_6H_4	5	$(CH_2)_6CH_3$	
218	3-CH_3O-C_6H_4	3-CH_3O-C_6H_4	H	$CH(CH_3)_2$	5	$(CH_2)_6CH_3$	
219	C_6H_{11}	C_6H_{11}	H	C_6H_5	5	$(CH_2)_6CH_3$	
220	C_6H_5	4-$(CH_3)_2N$-C_6H_4	H	$(CH_2)_7CH_3$	5	$(CH_2)_6CH_3$	
221	2-furanyl	2-furanyl	H	2,6-diClC_6H_3	5	$(CH_2)_6CH_3$	
222	4-(t-C_4H_9)C_6H_4	4-(t-C_4H_9)C_6H_4	H	CH_3	5	$(CH_2)_6CH_3$	
223	2-thienyl	2-thienyl	H	$(C_6H_4)(C_6H_5)$	5	$(CH_2)_6CH_3$	
224	4-HO-C_6H_4	4-HO-C_6H_4	CH_3	2,4-diFC_6H_3	5	$(CH_2)_6CH_3$	
225	$(CH_3)_2CH$	$(CH_3)_2CH$	CH_3	C_6H_{11}	5	$(CH_2)_6CH_3$	
226	C_6H_5-CH_2	C_6H_5-CH_2	CH_3	C_6H_5	5	$(CH_2)_6CH_3$	
227	C_6H_4-2-OCH_2O-2'-C_6H_4		H	2,4-diFC_6H_3	3	$(CH_2)_6CH_3$	
228		$C_6H_4OC_6H_4$	H	C_6H_{11}	3	$(CH_2)_6CH_3$	
229	4-CH_3O-C_6H_4	4-CH_3O-C_6H_4	H	2,4-diFC_6H_3	8	$(CH_2)_6CH_3$	
230	4-CH_3O-C_6H_4	4-$(CH_3)_2N$-C_6H_4	H	C_6H_{11}	8	$(CH_2)_6CH_3$	
231	4-CH_3O-C_6H_4	C_6H_{11}	H	2,4-diFC_6H_3	5	$(CH_2)_3CH_3$	
232	4-CH_3O-C_6H_4	$(CH_3)_2CH$	H	2,4-diFC_6H_3	5	$(CH_2)_8CH_3$	
233	4-$(CH_3)_2N$-C_6H_4	C_6H_{11}	H	2,4-diFC_6H_3	5	CH_3	
234	4-$(CH_3)_2N$-C_6H_4	$(CH_3)_2CH$	H	2,4-diFC_6H_3	5	C_6H_5	
235	C_6H_{11}	$(CH_3)_2CH$	CH_2CH_3	2,4-diFC_6H_3	5	3-F-C_6H_4	
236	C_6H_5	4-$CH_3OC_6H_4$	C_6H_5	$(CH_2)_7CH_3$	5	$(CH_2)_3CH_3$	

Table 1 (continued)

Ex. No.	R^1	R^2	R^3	R^4	n	R^6	mp°C
237	C_6H_5	4-$(CH_3)_2NC_6H_4$	$CH_2C_6H_5$	$(CH_2)_7CH_3$	5	C_6H_5	
238	C_6H_5	C_6H_{11}	H	n-C_3H_7	5	$(CH_2)_6CH_3$	
239	C_6H_5	$(CH_3)_2CH$	H	C_6H_{11}	5	$(CH_2)_6CH_3$	
240	4-$CH_3SC_6H_4$	4-$CH_3SC_6H_4$	H	2,4-di$CH_3OC_6H_3$	5	$(CH_2)_6CH_3$	
241	4-$CH_3SC_6H_4$	4-$CH_3SC_6H_4$	H	2,4,6-triFC_6H_2	5	$(CH_2)_6CH_3$	
242	4-$CH_3SO_2C_6H_4$	4-$CH_3SO_2C_6H_4$	H	3-FC_6H_4	5	$(CH_2)_6CH_3$	
243	C_6H_5	4-$CH_3SC_6H_4$	H	$CH(CH_3)_2$	5	$(CH_2)_6CH_3$	
244	C_6H_5	4-$CH_3SOC_6H_4$	H	C_6H_5	5	$(CH_2)_6CH_3$	
245	C_6H_5	4-$CH_3SO_2C_6H_4$	H	$(CH_2)_7CH_3$	5	$(CH_2)_6CH_3$	
246	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	n-C_3H_7	5	$(CH_2)_6CH_3$	
247	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	C_6H_{11}	5	$(CH_2)_6CH_3$	
248	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	C_6H_5	5	$(CH_2)_6CH_3$	
249	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	2,4-diFC_6H_3	3	$(CH_2)_6CH_3$	
250	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	C_6H_{11}	8	$(CH_2)_6CH_3$	
251	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	$(CH_2)_7CH_3$	5	C_6H_5	
252	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	n-C_3H_7	5	$(CH_2)_6CH_3$	
253	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	C_6H_{11}	5	$(CH_2)_6CH_3$	
254	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	C_6H_5	5	$(CH_2)_6CH_3$	
255	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	2,4-diFC_6H_3	3	$(CH_2)_6CH_3$	
256	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	C_6H_{11}	8	$(CH_2)_6CH_3$	
257	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	$(CH_2)_7CH_3$	5	C_6H_5	

Footnotes to Table 1

(a) ^1H NMR ($CDCl_3$) δ 11.6(s,1H), 7.7-7.1(m,10H), 4.4(t,1H,J=5Hz), 3.4(t,2H,J=6.7Hz), 3.2-2.9(m,5H), 1.8-1.0(m,29H), 1.0-0.8(m,7H).

(b) ^1H NMR ($CDCl_3$) δ 8.79-7.63(m,7H), 7.29-7.12(m,2H), 6.87-6.73(m,2H), 6.44(bs,1H), 3.34-3.08(m,6H), 1.83-1.18(m,16H), 0.86(t,3H).

(c) ^1H NMR ($CDCl_3$) δ 10.6-10.0(bs,1H), 7.80(m,1H),7.35-7.00(m,8H), 6.8-6.57(m,2H) 6.4(bs,1H), 3.89(t,2H), 3.25(t,2H), 3.00(t,2H) 2.33(s,3H), 2.32(s,3H), 1.79-1.29(m,16H), 0.88(t,3H).

(d) ^1H NMR ($CDCl_3$) δ 11.1-11.0(bs,1H), 7.64(m,1H), 7.5(d,2H), 7.27(m,6H), 6.75(m,1H), 6.53(m,1H), 6.33(bs,1H), 3.45(t,2H), 3.26(t,2H), 2.98(t,2H), 1.82-1.25(m,16H), 0.90(t,3H).

(e) ^1H NMR ($CDCl_3$) δ 10.8-10.7(m,1H), 8.0-7.2(m,7H), 6.9-6.6(m,2H), 6.0-5.9(m,1H), 3.4(t,2H,J=6.6Hz), 3.3(t,2H,J=7.6Hz), 3.0(t,2H,J=6.5Hz), 1.9-1.2(m,18H), 0.9(t,3H,J=7.2Hz).

(f) ^1H NMR ($CDCl_3$) δ 10.4-10.1(m,1H), 8.0-7.8(m,1H), 7.2-6.9(m,2H), 6.9-6.75(m,2H), 6.5-6.4(m,1H), 3.4-3.2(m,4H), 3.0(t,2H,J=7Hz), 1.9-1.1(m,19H), 0.9(t,3H,J=8Hz).

(g) ^1H NMR (DMSO-d_6) δ 12.17(bs,1H), 7.94(bs,1H), 7.43-6.77(m,11H), 3.57(s,3H), 3.24(m,4H), 3.19(s,3H), 3.07(t,2H), 1.76-1.18(m,16H), 0.85(t,3H).

(h) ^1H NMR ($CDCl_3$) δ 10.03-9.55(bs,1H), 7.86(m,1H), 7.58-7.20(bm, 4H), 6.82-6.61(m,6H), 6.42(bs,1H), 3.30-3.21(m,2H), 2.94(bs,14H), 1.78-1.26(m,16H), 0.88(t,3H).

(i) ^1H NMR ($CDCl_3$) δ 9.50-9.18(bs,1H), 7.97(m,1H), 6.80(m,2H),6.41(bs,1H), 3.31(m,4H), 2.86(t,2H), 2.68-2.37(m,2H), 1.91-1.13(m,36H), 0.89(t,3H).

(j) ^1H NMR ($CDCl_3$) δ 10.2-9.8(bs,1H), 7.85(m,1H), 7.70-7.16(m,7H), 6.75(m,1H), 6.89(d,3H), 6.39(bs,1H), 3.38(t,2H), 3.25(t,2H), 3.01(t,2H), 2.95(s,6H), 1.85-1.25(m,16H), 0.9(t,3H).

Footnotes to Table 1 (continued)

(k) ^{1}H NMR ($CDCl_3$) δ 10.35-10.15(bs,1H), 7.95(m,1H), 7.50-7.36(m,2H), 6.98-6.69(m,4H), 6.49-6.38(m,3H), 3.35(t,2H), 3.25(t,2H), 3.05(t,2H), 1.79-1.27(m,16H), 0.90(t,3H).

(l) ^{1}H NMR ($CDCl_3$) δ 7.47(d,4H), 6.84(d,4H), 4.12(d,1H), 3.84(m,1H), 3.80(s,6H), 3.33(t,2H), 3.07(t,2H), 2.96(t,2H), 1.8-1.24(m,16H), 1.08(d,6H), 0.90(t,3H).

(m) ^{1}H NMR ($CDCl_3$) δ 10.15-10.0(bs,1H), 7.82(m,1H), 7.53(m,2H), 7.31(m,6H), 6.73(m,1H), 6.61(m,1H), 3.4(t,2H), 3.26(t,2H), 3.00(t,2H), 1.82-1.49(m,12H), 1.33(bs,22H), 0.9(t,3H).

(n) ^{1}H NMR ($CDCl_3$) δ 10.8-10.76(bs,1H), 7.70(m,1H), 7.15(m,2H), 7.31(m,2H), 6.82(m,4H), 6.73(m,1H), 6.58(m,1H), 6.40(bs,1H), 3.8(s,6H), 3.46(t,2H), 3.01(s,3H), 2.94(t,2H), 1.78-1.44(m,6H).

(o) ^{1}H NMR ($CDCl_3$) δ 7.56-7.33(bs,4H), 6.67(d,4H), 4.11(d,1H), 3.89(m,1H), 3.3(t,2H), 3.08(t,2H), 2.95(bs,14H), 1.84-1.25(m,16H), 1.1(d,6H), 0.9(t,3H).

(p) ^{1}H NMR ($CDCl_3$) δ 7.7-6.9(m,14H), 4.1(t,1H,J=5.4Hz), 3.8-3.65(m,2H), 3.1-2.9(m,4H), 1.9-1.0(m,18H), 0.85(t,3H,J=6.7Hz).

(q) ^{1}H NMR (DMSO-d_6) δ 11.58(s,1H), 5.71(d,1H), 3.75(m,1H), 3.07(t,4H), 2.95-2.78(m,4H), 1.57-1.1(m,16H), 1.14(d,6H), 1.10(d,6H), 1.03(d,6H), 0.85(t,3H).

EXAMPLE 267

Preparation of N'-(2,4-difluorophenyl)-N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptylthiourea

Employing the method of Example 1, Part E, using 2,4-difluorophenylisothiocyanate (0.14 g, 0.0008 mol), the title compound (0.19 g, 0.00031 mol) was obtained as a white solid, mp 116-118°. ^{1}H NMR ($CDCl_3$) δ 9.5-9.4(s,1H), 7.8-7.1(m,11H), 7.0-6.7(m,3H), 3.8(t,2H,J=7.6Hz), 3.6(t,2H,J=7.8Hz), 3.1-(t,2H,J=7Hz), 1.9-1.1(m,18H), 0.9(t,3H,J=4Hz).

EXAMPLE 269

Preparation of N'-(2,4-difluorophenyl)-N-[5-(4,5-diphenyl-1H-imidazol-2-ylsulfinyl)pentyl]-N-heptylurea

To a solution of N'-(2,4-difluorophenyl)-N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptylurea (0.59 g, 0.001 mol) in methylene chloride (50 mL) cooled to -78° was added, dropwise, a solution of meta-chloroperbenzoic acid (0.286 g, 0.0017 mol) in methylene chloride (10 mL). The reaction mixture was stirred at -78° for 1 hour and then allowed to warm to ambient temperature. The reaction mixture was then cooled to 0° and then added, dropwise, was a solution of saturated sodium bisulfite. The layers were separated

and the organic layer was washed with saturated sodium bisulfite. The layers were separated and the sodium chloride solution, dried over magnesium sulfate, and concentrated under vacuum. The residue (0.76 g) was chromatographed with 1:1 hexane-ethyl acetate to give the title compound (0.43 g, 0.00071 mol) as a yellow solid, mp 77-79°. ^{1}H NMR ($CDCl_3$) δ 8.1-7.9(m,1H), 7.6-7.2 (m,10H), 6.9-6.7(m,2H), 6.4-(d,1H,J = 3.3Hz), 3.4-3.1(m,6H), 2.0-1.1(m,18H), 0.9(t,3H,J = 6.4Hz).

EXAMPLE 272

Preparation of N'-(2,4-difluorophenyl)-N-[5-[(4,5-diphenyl-1H-imidazol-2-yl)sulfonyl]pentyl]-N-heptylurea

To a solution of N'-(2,4-difluorophenyl)-N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptylurea (0.11 g, 0.00019 mol) in methanol (5 mL) was added, portionwise as a solid, Oxone™ (0.234 g, 0.00038 mol) and the reaction mixture was stirred at ambient temperature for 7 hours. The solids were filtered and washed with methanol. The filtrate was concentrated under vacuum and the residue was chromatographed with 6:4 hexane-ethyl acetate to give the title compound (0.06 g, 0.000096 mol) as a glassy, colorless solid, mp 66-68°. ^{1}H NMR ($CDCl_3$) δ 7.85-7.75(m,1H), 7.6-7.1(m,11H), 6.8-6.6(m,2H), 6.4(s,1H), 3.4(t,4H,J = 10Hz), 3.25(t,2H,J = 7Hz), 1.9-1.75(m,2H), 1.75-1.4(m,6H), 1.4-1.1(m,8H), 0.9(t,3H,J = 8Hz).

EXAMPLE 329

Preparation of N'-(2,4-difluorophenyl)-N-[5-(4,5-diphenyl-1H-imidazol-2-ylamino)phenyl]-N-heptylurea

Part A. A solution of 2-bromo-4,5-diphenyl-1H-imidazole (3,5 g, 0.0117 mol) in 1,5-diaminopentane (20 mL) was heated to reflux for 48 hours. The reaction mixture was concentrated in vacuo to give a viscous oil which was taken up in methylene chloride (60 mL) and washed with 10% aqueous $NaHCO_3$, water (2 x 50 mL), brine, dried over magnesium sulfate and concentrated in vacuo to give 5-(4,5-diphenyl-1H-imidazol-2-ylamino)aminopentane as a viscous oil (3.5 g, 0.0109 mol). ^{1}H NMR ($CDCl_3$) δ 7.55-7.09-(m,10H), 4.79-3.79(bs,3H), 3.14(t,2H), 2.59(t,2H), 1.79-1.22(m,6H).

Part B. To a solution of 5-(4,5-diphenyl-1H-imidazol-2-ylamino)aminopentane (1.7 g, 0.00531 mol) and triethylamine (0.58 g, 0.0058 mol) in methylene chloride cooled to 0° under a nitrogen atmosphere, heptanoyl chloride (0.788 g, 0.00531 mol) was added slowly. The reaction mixture was stirred for 1 hour at 0°, poured into water and extracted with methylene chloride (2 x 50 mL). The combined organic extract was washed with water, brine, dried over magnesium sulfate and concentrated to give N-[5-(4,5-diphenyl-1H-imidazol-2-ylamino)pentyl]heptanamide as a viscous oil. The product was purified by flash chromatography on silica gel (250 mL) eluting methylene chloride:methanol (95:5 v:v), to give an amber foam (1.3 g, 0.003 mol). ^{1}H NMR ($CDCl_3$) δ 7.43-7.15(m,10H), 6.3(m,1H), 3.24-3.1(m,4H), 2.09-(t,2H), 1.6-1.16(m,14H), 0.84(t,3H).

Part C. Employing the method of Example 118, Part B, but using N-[5-(4,5-diphenyl-1H-imidazol-2-ylamino)pentyl]heptanamide, N-[5-(4,5-diphenyl-1H-imidazol-2-ylamino)pentyl]-N-heptylamine was obtained as an amber oil (1.00 g, 0.00238 mol). ^{1}H NMR ($CDCl_3$) δ7.56-6.85(m,10H), 3.23(m,2H), 2.49-(m,4H), 1.68-0.90(m,16H), 0.88(t,3H).

Part D. Employing the method of Example 118, Part C, but using N-[5-(4,5-diphenyl-1H-imidazol-2-ylamino)pentyl]-N-heptylamine, the title compound was obtained as a yellow foam (0.395 g, 0.000688 mol). ^{1}H NMR ($CDCl_3$) δ 8.37-7.1(m,11H), 6.9-6.67(m,2H), 6.44(d,1H),4.53(bs,1H), 3.27(m,6H), 1.74-1.23-(m,16H), 0.89(t,3H).

EXAMPLE 330

Preparation of N'-(2,4-difluorophenyl)-N-[6-(4,5-diphenyl-1H-imidazol-2-yl)hexyl]-N-heptylurea

Part A. To a solution of 4,5-diphenyl-1-[(trimethylsilyl)ethoxymethyl]-1H-imidazole (2.5 g, 0.00734 mol) (B. Lipshutz, B. Huff, W. Hazen, Tetrahedron Letters, 29, 3411-14, 1988), in dry tetrahydrofuran (50 mL) cooled to -78° under a nitrogen atmosphere, n-butyl lithium in hexane (2.5 M, 0.00734 mol) was added slowly. The reaction mixture was stirred for 1 hour and 1,6-dibromohexane (2.68 g, 0.0011 mol) was added rapidly, stirred for 1/2 hour and was allowed to warm to ambient temperature and stirred for 2 additional hours. The reaction mixture was poured into water and extracted with ethyl acetate (2 x 50 mL). The combined organic layer was washed with water, brine, dried over magnesium sulfate and concentrated to give a viscous oil. The product was purified by flash chromatography on silica gel (250

mL) eluting with hexane:ethyl acetate (70:30 v:v) to give 6-bromo-1-(4,5-diphenyl-1-[(trimethylsilyl)-ethoxymethyl]imidazol-2-yl)hexane as an oil (2.18 g, 0.00424 mol). ^{1}H NMR ($CDCl_3$) δ 7.53-7.16(m,10H), 5.10(s,2H), 3.48(t,2H), 3.34(t,2H), 2.90(t,2H), 1.99-1.5(m,8H), 0.875(t,2H), 0.008(s,9H).

Part B. A solution of 6-bromo-1-(4,5-diphenyl-1-[(trimethylsilyl)ethoxymethyl]-1H-imidazol-2-yl)hexane (1.0 g, 0.00195 mol) and n-heptylamine (0.45 g, 0.00389 mol) in acetonitrile (25 mL) was heated to 60 ° for 8 hours. The reaction mixture was poured into 10% aqueous sodium bicarbonate and extracted with ethyl acetate (2 x 50 mL). The combined organic extract was washed with water, brine, dried over magnesium sulfate and concentrated to give N-[6-(4,5-diphenyl-1-[(trimethylsilyl)ethoxymethyl]-1H-imidazol-2-yl)hexyl]-N-heptylamine as a colorless viscous oil (1.04 g, 0.00189 mol). ^{1}H NMR ($CDCl_3$) δ 7.52-7.2(m,10H), 5.11(s,2H), 4.7-4.2(bs,1H), 3.3(t,2H), 2.93-2.70(m,6H), 1.95-1.34(m,18H), 0.93(t,3H), 0.86-(t,2H), 0.005(s,9H).

Part C. Employing the method of Example 118, Part C, but using N-[6-(4,5-diphenyl-1-[(trimethylsilyl)-ethoxymethyl]-imidazole-2-yl)hexyl]-N-heptylamine, N'-(2,4-difluorophenyl)-N-[6-(4,5-diphenyl-1-[-(trimethylsilyl)ethoxymethyl]-imidazole-2-yl)hexyl]-N-heptylurea was isolated as a viscous oil (1.40 g, 0.00199 mol). ^{1}H NMR ($CDCl_3$) δ 8.12(m,1H), 7.53-7.16(m,10H), 6.88(m,2H), 6.48(d,1H), 5.1(s,2H), 3.33-(m,6H), 2.90(t,2H), 2.0-1.34(m,18H), 0.88(t,3H), 0.79(t,2H), 0.055(s,9H).

Part D. To a solution of N'-(2,4-difluorophenyl)-N-[6-(4,5-diphenyl-1-[(trimethylsilyl)ethoxymethyl]-1H-imidazol-2-yl)hexyl]-N-heptylurea (0.60 g, 0.000853 mol) in dry tetrahydrofuran (10 mL) under a nitrogen atmosphere, tetrabutylammonium fluoride (1M in tetrahydrofuran, 3.41 mL) was added and the reaction mixture was heated to reflux 7 hours. The reaction mixture was cooled, poured into water (50 mL) and extracted with ethyl acetate (2x50 mL). The combined organic layer was washed with water, brine, dried over magnesium sulfate and concentrated in vacuo. The product was purified by flash chromatography on silica gel (75 mL) eluting hexane:ethyl acetate (60:40 v:v) to give the title compound as a colorless glass (0.26 g, 0.000454 mol). ^{1}H NMR ($CDCl_3$) δ 9.5-9.0(bs,1H), 7.87(m,1H), 7.5-7.2(m,10H), 6.83-6.7-(m,2H), 6.4(d,1H), 3.28(m,4H), 2.67(t,2H), 1.75-1.26(m,18H), 0.88(t,3H).

Table 2

Ex. No.	R^1	R^2	R^3	R^4	X	Y	n	R^6	mp°C
258	C_6H_5	C_6H_5	H	2,4-diFC_6H_3	O	O	5	$(CH_2)_6CH_3$	
259	C_6H_5	C_6H_5	H	2,4-di$CH_3OC_6H_3$	O	O	5	$(CH_2)_6CH_3$	
260	C_6H_5	C_6H_5	H	2,4-diFC_6H_3	O	O	8	$(CH_2)_6CH_3$	
261	C_6H_5	C_6H_5	H	n-C_3H_7	O	O	8	$(CH_2)_6CH_3$	
262	C_6H_5	C_6H_5	H	2,4-diFC_6H_3	O	S	5	$(CH_2)_6CH_3$	
263	C_6H_5	C_6H_5	CH_3	2,4-diFC_6H_3	O	O	8	$(CH_2)_6CH_3$	
264	C_6H_5	C_6H_5	C_6H_5	2,4,6-triFC_6H_2	O	O	8	$(CH_2)_6CH_3$	
265	4-FC_6H_4	4-FC_6H_4	H	2,4,6-triFC_6H_2	O	O	5	$(CH_2)_6CH_3$	
266	C_6H_5	3-pyridinyl	H	2,4-diFC_6H_3	O	O	5	$(CH_2)_6CH_3$	
267	C_6H_5	C_6H_5	H	2,4-diFC_6H_3	S	S	5	$(CH_2)_6CH_3$	116-118
268	4-FC_6H_4	4-FC_6H_4	H	2,4-diFC_6H_3	S	S	8	$(CH_2)_6CH_3$	

Table 2 (continued)

Ex. No.	R^1	R^2	R^3	R^4	X	Y	n	R^6	mp°C
269	C_6H_5	C_6H_5	H	2,4-diFC_6H_3	SO	0	5	$(CH_2)_6CH_3$	77-79
270	C_6H_5	C_6H_5	H	2,4-diFC_6H_3	SO	0	8	$(CH_2)_6CH_3$	
271	C_6H_5	C_6H_5	H	n-C_3H_7	SO	0	5	$(CH_2)_6CH_3$	
272	C_6H_5	C_6H_5	H	2,4-diFC_6H_3	SO_2	0	5	$(CH_2)_6CH_3$	66-68
273	C_6H_5	C_6H_5	H	2,4-diFC_6H_3	SO_2	0	8	$(CH_2)_6CH_3$	
274	C_6H_5	C_6H_5	H	n-C_3H_7	SO_2	0	8	$(CH_2)_6CH_3$	
275	C_6H_5	C_6H_5	H	n-C_3H_7	SO_2	S	5	$(CH_2)_6CH_3$	
276	C_6H_5	C_6H_5	CH_3	n-C_3H_7	SO_2	0	5	$(CH_2)_6CH_3$	
277	C_6H_5	C_6H_5	H	2,4,6-triFC_6H_2	NH	0	5	$(CH_2)_6CH_3$	
278	C_6H_5	C_6H_5	H	2,4-di$CH_3OC_6H_3$	NH	0	5	$(CH_2)_6CH_3$	
279	C_6H_5	C_6H_5	H	2,4-diFC_6H_3	NH	0	8	$(CH_2)_6CH_3$	
280	4-FC_6H_4	4-FC_6H_4	H	n-C_5H_{11}	NH	0	4	$(CH_2)_8CH_3$	
281	C_6H_5	C_6H_5	CH_3	C_6H_5	NH	0	7	$(CH_2)_5CH_3$	
282	C_6H_5	C_6H_5	H	2,4-diFC_6H_3	NCH_3	0	5	$(CH_2)_6CH_3$	
283	C_6H_5	C_6H_5	H	2,4-diFC_6H_3	NCH_3	0	8	$(CH_2)_6CH_3$	
284	C_6H_5	C_6H_5	H	n-C_3H_7	$NCH_2C_6H_5$	0	6	$(CH_2)_8CH_3$	
285	C_6H_5	C_6H_5	H	2,4,6-triFC_6H_2	$NCH_2C_6H_5$	0	5	$(CH_2)_6CH_3$	
286	C_6H_5	C_6H_5	H	2,4-diClC_6H_3	NC_3H_7	0	8	$(CH_2)_6CH_3$	
287	C_6H_5	C_6H_5	H	3,4,5-tri$CH_3OC_6H_2$	NC_3H_7	0	4	$(CH_2)_5CH_3$	

Table 2 (continued)

Ex. No.	R^1	R^2	R^3	R^4	X	Y	n	R^6	mp°C
288	C_6H_5	C_6H_5	H	CH_3	NC_6H_{13}	0	5	$(CH_2)_6CH_3$	
289	C_6H_5	C_6H_5	H	2,4,6-triFC_6H_2	S	S	5	$(CH_2)_6CH_3$	124-126
290	C_6H_5	C_6H_5	H	$(CH_2)_2CH_3$	S	S	5	$(CH_2)_6CH_3$	89-91
291	C_6H_5	C_6H_5	H	3-FC_6H_4	S	S	5	$(CH_2)_6CH_3$	161-163
292	$(CH_3)_2CH$	$(CH_3)_2CH$	H	C_6H_{11}	NH	0	5	$(CH_2)_6CH_3$	
293	$(CH_3)_2CH$	C_6H_5	H	2,4-di$CH_3OC_6H_3$	CH_2	0	5	$(CH_2)_6CH_3$	
294	4-$CH_3OC_6H_4$	C_6H_5	H	2,4,6-triFC_6H_2	SO	0	5	$(CH_2)_6CH_3$	
295	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	3-FC_6H_4	SO_2	0	5	$(CH_2)_6CH_3$	
296	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	$CH(CH_3)_2$	O	S	5	$(CH_2)_6CH_3$	
297	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	C_6H_5	NH	S	5	$(CH_2)_6CH_3$	
298	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	$(CH_2)_7CH_3$	CH_2	S	5	$(CH_2)_6CH_3$	
299	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	2,6-diClC_6H_3	O	0	5	$(CH_2)_6CH_3$	
300	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	CH_3	NH	0	5	$(CH_2)_6CH_3$	
301	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	$(C_6H_4)(C_6H_5)$	CH_2	0	5	$(CH_2)_6CH_3$	
302	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	CH_3	2,4-diFC_6H_3	SO	0	5	$(CH_2)_6CH_3$	
303	$(CH_3)_2CH$	$(CH_3)_2CH$	CH_3	C_6H_{11}	SO_2	0	5	$(CH_2)_6CH_3$	
304	$(CH_3)_2CH$	$(CH_3)_2CH$	CH_3	C_6H_5	O	H_2	5	$(CH_2)_6CH_3$	
305	C_6H_5	C_6H_5	H	2,4-diFC_6H_3	NH	H_2	3	$(CH_2)_6CH_3$	
306	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	C_6H_{11}	CH_2	H_2	3	$(CH_2)_6CH_3$	
307	C_6H_5	C_6H_5	H	n-C_3H_7	O	S	5	$(CH_2)_6CH_3$	

Table 2 (continued)

Ex. No.	R^1	R^2	R^3	R^4	X	Y	n	R^6	mp°C
308	$(CH_3)_2CH$	$(CH_3)_2CH$	H	C_6H_{11}	NH	S	5	$(CH_2)_6CH_3$	
309	$(CH_3)_2CH$	C_6H_5	H	$CH(CH_3)_2$	CH_2	S	5	$(CH_2)_6CH_3$	
310	C_6H_5	4-$CH_3OC_6H_4$	H	C_6H_5	O	H_2	5	$(CH_2)_6CH_3$	
311	$(CH_3)_2CH$	$(CH_3)_2CH$	H	2,4-diFC_6H_3	NH	H_2	3	$(CH_2)_6CH_3$	
312	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	C_6H_{11}	CH_2	H_2	8	$(CH_2)_6CH_3$	
313	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	$(CH_2)_7CH_3$	SO	O	5	C_6H_5	
314	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	n-C_3H_7	SO_2	O	5	$(CH_2)_6CH_3$	
315	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	C_6H_{11}	NH	O	5	$(CH_2)_6CH_3$	
316	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	$CH(CH_3)_2$	CH_2	O	5	$(CH_2)_6CH_3$	
317	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	C_6H_5	CH_2	S	5	$(CH_2)_6CH_3$	
318	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	2,4-diFC_6H_3	S	H_2	3	$(CH_2)_6CH_3$	
319	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	C_6H_{11}	S	H_2	8	$(CH_2)_6CH_3$	
320	C_6H_5	C_6H_5	C_6H_5	$(CH_2)_7CH_3$	S	H_2	5	C_6H_5	
321	C_6H_5	C_6H_5	CH_2CH_3	2,4-diFC_6H_3	S	H_2	5	$(CH_2)_6CH_3$	
322	$(CH_3)_2CH$	$(CH_3)_2CH$	$CH_2C_6H_5$	2,4-diFC_6H_3	S	H_2	5	$(CH_2)_6CH_3$	
323	4-$CH_3SC_6H_4$	4-$CH_3SC_6H_4$	H	2,4-diFC_6H_3	S	O	8	$(CH_2)_6CH_3$	
324	4-$CH_3SOC_6H_4$	4-$CH_3SOC_6H_4$	H	C_6H_{11}	O	H_2	8	$(CH_2)_6CH_3$	
325	4-$CH_3SO_2C_6H_4$	4-$CH_3SO_2C_6H_4$	H	2,4-diFC_6H_3	CH_2	S	5	$(CH_2)_3CH_3$	
326	4-$CH_3SC_6H_4$	C_6H_5	H	2,4-diFC_6H_3	NH	O	5	$(CH_2)_8CH_3$	

Table 2 (continued)

Ex. No.	R^1	R^2	R^3	R^4	X	Y	n	R^6	mp°C
327	4-$CH_3SOC_6H_4$	C_6H_5	H	2,4-diFC_6H_3	S	H_2	5	CH_3	
328	4-$CH_3SO_2C_6H_4$	C_6H_5	H	2,4-diFC_6H_3	S	S	5	C_6H_5	
329	C_6H_5	C_6H_5	H	2,4-diFC_6H_3	NH	O	5	$(CH_2)_6CH_3$	foam
330	C_6H_5	C_6H_5	H	2,4-diFC_6H_3	CH_2	O	5	$(CH_2)_6CH_3$	glass

EXAMPLE 331

Preparation of 2,4-difluoro-N-[(5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl)]-N-heptylbenzeneacetamide

To a solution of N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-1-heptanamine (2.2 g, 0.005 mol), 1-hydroxybenzotriazole hydrate (0.81 g, 0.006 mol), and 2,4-difluorophenylacetic acid (1.12 g, 0.0065 mol) in

N,N-dimethylformamide (50 mL) at 0° was added, portionwise as a solid, dicyclohexylcarbodiimide (1.24 g, 0.006 mol). The reaction mixture was stirred at 0° for 2.5 hours, then at ambient temperature for 72 hours. The solids were filtered and washed with chloroform. The filtrate was concentrated under vacuum and the residue (5.2 g) was chromatographed with 7:3 hexane-ethyl acetate. The resulting solid was triturated with hexane to give the title compound (2.59 g, 0.0044 mol) as a yellow oil, ^{1}H NMR ($CDCl_3$) δ 7.6-7.0(m,11H), 6.8-6.5(m,2H), 3.7(d,2H,J = 13.7Hz), 3.5(t,2H,J = 6.4Hz), 3.4-3.0(m,3H), 2.9(t,2H,J = 6.1Hz), 1.8-1.1(m,17H), 0.9(t,3H,J = 6.6Hz).

EXAMPLE 344

Preparation of N-[5-[4,5-bis(4-methoxyphenyl)-1H-imidazol-2-ylthio]pentyl]-2,4-difluoro-N-heptylbenzeneethanamine

To a solution of lithium aluminium hydride (1 N in tetrahydrofuran, 2 mL) in dry tetrahydrofuran (30 mL), a solution of N-[5-[4,5-bis(4-methoxyphenyl)-1H-imidazol-2-ylthio]pentyl]-2,4-difluoro-N-heptylbenzeneacetamide (0.70 g, 0.00107 mol) in dry tetrahydrofuran (15 mL) was added slowly. The reaction mixture was heated to reflux for 5 hours and was then allowed to cool to ambient temperature. The reaction mixture was poured into a mixture of 10% aqueous sodium sulfate (150 mL) and ice (150 mL). The resultant emulsion was filtered through Celite® and the filtrate was extracted with ethyl acetate (3 x 100 mL). The organic layer was washed with water, brine, dried over magnesium sulfate and concentrated in vacuo to give a crude oil. The product was purified by flash chromatography on silica gel (100 mL) eluting methanol: methylene chloride (5.95 v:v) to give the title compound as a viscous colorless oil (0.46 g, 0.000723 mol). ^{1}H NMR ($CDCl_3$) δ 9.2-9.15(bs,1H), 7.56-7.25(m,4H), 7.11(m,1H), 6.94-6.70(m,6H), 3.81(m,6H), 3.07(t,2H), 2.74-2.58(m,4H), 2.43(m,4H), 1.71(m,2H), 1.53-1.20(m,14H), 0.91(t,3H).

EXAMPLE 346

Preparation of N-[5-[4,5-bis(4-methoxyphenyl)-1H-imidazol-2-ylthio]pentyl]-N-heptylcyclohexaneacetamide

Part A. Employing the method of Example 118, Part C, but using 2-cyclohexane acetyl chloride, N-heptyl-N-(5-hydroxypentyl)cyclohexaneacetamide was obtained as an oil (1.5 g, 0.0046 mol). ^{1}H NMR ($CDCl_3$) δ 3.70-3.61(m,2H), 3.37-3.18(m,4H), 2.03(d,2H), 1.97-1.08(m,26H), 1.02-0.86(m,4H).

Part B. Employing the method of Example 118, Part D, but using N-heptyl-N-(5-hydroxypentyl)-cyclohexaneacetamide, N-(5-bromopentyl)-N-heptylcyclohexane acetamide was isolated as an oil (1.3 g, 0.00334 mol). ^{1}H NMR ($CDCl_3$) δ 3.47-3.39(m,2H), 3.36-3.18(m,4H), 2.17(d,2H), 1.96-0.86(m,30H).

Part C. Employing the method of Example 118, Part E, but using N-(5-bromopentyl)-N-heptylcyclohexaneacetamide, the title compound was isolated as an oil (0.47 g, 0.00075 mol), ^{1}H NMR (DMSO-d_6) δ 12.34(s,1H), 7.29(d,2H), 6.95(d,2H), 6.84(d,2H), 3.77(s,3H), 3.73(s,3H), 3.18(m,4H) 3.07(m,2H), 2.09(d,2H), 1.73-0.81(m,30H).

Additional amides, which are listed in Table 3, were prepared or could be prepared analogously according to the procedures of Examples 331, 344 and 346.

Table 3

Ex. No.	R^1	R^2	R^3	R^4	X	Y	n	R^6	mp°C
331	C_6H_5	C_6H_5	H	CH_2-2,4-diFC_6H_3	S	O	5	$(CH_2)_6CH_3$	oil
332	C_6H_5	C_6H_5	H	$CH_2CH_2CH_3$	S	O	5	$(CH_2)_6CH_3$	oil(a)
333	C_6H_5	C_6H_5	H	$CH_2(CH_2)_2CH_3$	S	O	5	$(CH_2)_6CH_3$	oil(b)
334	C_6H_5	C_6H_5	H	$CH_2(C_6H_4)(C_6H_5)$	S	O	5	$(CH_2)_6CH_3$	57-58
335	C_6H_5	C_6H_5	H	$CH_2C_6H_{11}$	S	O	5	$(CH_2)_6CH_3$	oil(c)
336	C_6H_5	C_6H_5	H	2,4-diFC_6H_3	S	O	5	$(CH_2)_6CH_3$	oil(d)
337	C_6H_5	C_6H_5	H	C_6H_5	S	O	5	$(Cl_2)_6CH_3$	oil(e)
338	$(CH_3)_2CH$	$(CH_3)_2CH$	H	CH_2-C_6H_{11}	S	O	5	$(CH_2)_6CH_3$	oil(f)
339	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	$(CH_2)_2CH_3$	S	O	5	$(CH_2)_6CH_3$	oil(g)
340	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	CH_2-3,4-diClC_6H_3	S	O	5	$(CH_2)_6CH_3$	oil(h)
341	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	CH_2-C_6F_5	S	O	5	$(CH_2)_6CH_3$	oil(i)

Table 3 (continued

Ex. No.	R^1	R^2	R^3	R^4	X	Y	n	R^6	mp°C
342	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	CH_2-2,4-diFC_6H_3	S	O	5	$(CH_2)_6CH_3$	oil(j)
343	C_6H_5	C_6H_5	H	$(CH_2)_2CH_3$	S	H_2	5	$(CH_2)_6CH_3$	oil(k)
344	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	CH_2-2,4-diFC_6H_3	S	H_2	5	$(CH_2)_6CH_3$	oil
345	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	$CH_2C_6H_{11}$	S	O	5	$(CH_2)_6CH_3$	oil(l)
346	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	$CH_2C_6H_{11}$	S	O	5	$(CH_2)_6CH$	oil
347	n-C_3H_7	n-C_3H_7	H	n-C_3H_7	S	O	5	$(CH_2)_6CH_3$	
348	3-pyridinyl	3-pyridinyl	H	CH_2-2,4-di$CH_3OC_6H_3$	CH_2	O	5	$(CH_2)_6CH_3$	
349	4-pyridinyl	4-pyridinyl	H	CH_2-2,4,6-triFC_6H_2	NH	O	5	$(CH_2)_6CH_3$	
350	2-$CH_3OC_6H_4$	2-$CH_3OC_6H_4$	H	CH_2-3-FC_6H_4	S	H_2	5	$(CH_2)_6CH_3$	
351	3-$CH_3OC_6H_4$	3-$CH_3OC_6H_4$	H	$CH(CH_3)_2$	O	O	5	$(CH_2)_6CH_3$	
352	C_6H_{11}	C_6H_{11}	H	C_6H_5	CH_2	O	5	$(CH_2)_6CH_3$	
353	C_6H_5	4-$(CH_3)_2NC_6H_4$	H	$(CH_2)_7CH_3$	NH	O	5	$(CH_2)_6CH_3$	
354	2-furanyl	2-furanyl	H	2,6-diClC_6H_3	S	O	5	$(CH_2)_6CH_3$	
355	4-(t-C_4H_9)C_6H_4	4-(t-C_4H_9)C_6H_4	H	CH_3	O	H_2	5	$(CH_2)_6CH_3$	
356	2-thienyl	2-thienyl	H	$CH_2(C_6H_4)(C_6H_5)$	CH_2	O	5	$(CH_2)_6CH_3$	
357	4-HOC_6H_4	4-HOC_6H_4	CH_3	2,4-diFC_6H_3	NH	O	5	$(CH_2)_6CH_3$	
358	$(CH_3)_2CH$	$(CH_3)_2CH$	CH_3	C_6H_{11}	S	O	5	$(CH_2)_6CH_3$	
359	$C_6H_5CH_2$	$C_6H_5CH_2$	CH_3	C_6H_5	O	O	5	$(CH_2)_6CH_3$	
360	C_6H_4-2-OCH_2O-2'-C_6H_4		H	2,4-diFC_6H_3	CH_2	H_2	3	$(CH_2)_6CH_3$	

Table 3 (continued

Ex. No.	R^1	R^2	R^3	R^4	X	Y	n	R^6	mp°C
361	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	H	2,4-diFC_6H_3	S	0	8	$(CH_2)_6CH_3$	
362	4-$CH_3OC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	C_6H_{11}	O	0	8	$(CH_2)_6CH_3$	
363	4-$CH_3OC_6H_4$	C_6H_{11}	H	CH_2-2,4-diFC_6H_3	CH_2	O	5	$(CH_2)_3CH_3$	
364	4-$CH_3OC_6H_4$	$(CH_3)_2CH$	H	CH_2-2,4-diFC_6H_3	NH	H_2	5	$(CH)_8CH_3$	
365	4-$(CH_3)_2NC_6H_4$	C_6H_{11}	H	2,4-diFC_6H_3	S	O	5	CH_3	
366	4-$(CH_3)_2NC_6H_4$	$(CH_3)_2CH$	H	CH_2-2,4-diFC_6H_3	O	O	5	C_6H_5	
367	$C_6H_4OC_6H_4$		H	C_6H_{11}	NH	O	3	$(CH_2)_6CH_3$	
368	C_6H_5	4-$CH_3OC_6H_4$	$CH_2C_6H_5$	$(CH_2)_7CH_3$	NH	O	5	$(CH_2)_3CH_3$	
369	C_6H_5	4-$(CH_3)_2NC_6H_4$	C_6H_5	$(CH_2)_7CH_3$	S	H_2	5	C_6H_5	
370	$(CH_3)CH$	$(CH_3)_2CH$	H	2,4-diFC_6H_3	S	O	5	$(CH_2)_6CH_3$	
371	4-$CH_3SC_6H_4$	4-$CH_3SC_6H_4$	H	CH_2-2,4-diFC_6H_3	S	O	5	$(CH_2)_6CH_3$	
372	4-$CH_3SOC_6H_4$	4-$CH_3SOC_6H_4$	H	CH_2-2,4-diFC_6H_3	NH	O	5	$(CH_2)_6CH_3$	
373	4-$CH_3SO_2C_6H_4$	4-$CH_3SO_2C_6H_4$	H	CH_2-2,4-diFC_6H_3	CH_2	O	5	$(CH_2)_6CH_3$	
374	C_6H_5	4-$CH_3SC_6H_4$	H	CH_2-2,4-diFC_6H_3	S	O	5	$(CH_2)_6CH_3$	
375	C_6H_5	4-$CH_3SOC_6H_4$	H	CH_2-2,4-diFC_6H_3	NH	O	5	$(CH_2)_6CH_3$	
376	C_6H_5	4-$CH_3SO_2C_6H_4$	H	CH_2-2,4-diFC_6H_3	CH_2	O	5	$(CH_2)_6CH_3$	
377	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	CH_3	n-C_3H_7	S	O	5	$(CH_2)_6CH_3$	
378	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	$CH_2C_6H_{11}$	SO	O	5	$(CH_2)_6CH_3$	
379	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	$CH(CH_3)_2$	S	O	5	$(CH_2)_6CH_3$	

Table 3 (continued)

Ex. No.	R^1	R^2	R^3	R^4	X	Y	n	R^6	mp°C
380	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	$CH_2C_6H_5$	S	O	5	$(CH_2)_6CH_3$	
381	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	CH_2-2,4-diFC_6H_3	S	S	3	$(CH_2)_6CH_3$	
382	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	$CH_2C_6H_{11}$	S	O	8	$(CH_2)_6CH_3$	
383	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	$(CH_2)_7CH_3$	S	O	5	C_6H_5	
384	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	n-C_3H_7	SO_2	O	5	$(CH_2)_6CH_3$	
385	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	C_6H_{11}	S	O	5	$(CH_2)_6CH_3$	
386	4$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	$CH(CH_3)_2$	S	H_2	5	$(CH_2)_6CH_3$	
387	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	C_6H_5	S	O	5	$(CH_2)_6CH_3$	
388	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	2,4-diFC_6H_3	SO	O	3	$(CH_2)_6CH_3$	
389	4-$(CH_3)_2C_6H_4$	4-$(CH_3)_2NC_6H_4$	H	C_6H_{11}	S	O	8	$(CH_2)_6CH_3$	
390	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	$(CH_2)_7CH_3$	SO_2	O	5	C_6H_5	

Footnotes To Table 3

(a) ^{1}H NMR ($CDCl_3$) δ 11.7-11.6(bs,1H), 7.7-7.1(m,10H), 3.4(t,2H,J=7Hz), 3.3-3.2(m,2H), 2.9(t,2H,J=7Hz), 2.35-2.25(m,2H), 1.8-1.1(m,18H), 1.0-0.8(m,6H).

(b) ^{1}H NMR ($CDCl_3$) δ 11.8-11.7(bs,1H), 7.7-7.1(m,10H), 3.4(t,2H,J=6.6Hz), 3.2(t,2H,J=8.7), 2.9(t,2H,J=6.5Hz), 2.4-2.2(m,2H), 1.8-1.1(m,20H), 0.85(sextet, 6H,J=4.1Hz).

(c) ^{1}H NMR ($CDCl_3$) δ 7.6-7.1(m,11H), 3.4-2.9(m,6H), 2.2-2.1(m,2H), 1.8-1.0(m,27H), 0.9-0.8(m,3H).

(d) ^{1}H NMR ($CDCl_3$) δ 7.6-7.2(m,11H), 6.9-6.8(m,2H), 3.7-3.4(m,2H), 3.2-3.0(m,4H), 1.9-1.0(m,17H).

(e) ^{1}H NMR ($CDCl_3$) δ 7.6-7.1(m,16H), 3.6-3.4(m,2H), 3.3-2.9(m,4H), 1.9-1.0(m,16H), 0.9-0.8(m,3H).

(f) ^{1}H NMR (DMSO-d_6) δ 11.64(bs,1H), 3.18(m,4H), 2.98-2.74(m,4H), 2.08(d,2H), 1.77-0.81(m,42H).

(g) ^{1}H NMR (DMSO-d_6) δ 12.36(s,1H), 7.39(d,2H), 7.31(d,2H), 6.95(d,2H), 6.85(d,2H), 3.76(s,3H), 3.74(s,3H), 3.28-3.03(m,6H), 2.22(t,2H), 1.75-1.11(m,18H), 0.83(m,6H).

(h) ^{1}H NMR (DMSO-d_6) δ 12.35(bs,1H), 7.62-7.17(m,7H), 6.95(d,2H), 6.85(d,2H), 3.8-3.66(m,8H), 3.35-3.02(m,6H), 1.78-1.14(m,16H), 0.85(m,3H).

(i) ^{1}H NMR (DMSO-d_6) δ 12.33(bs,1H), 7.37(d,2H), 7.31(d,2H), 6.94(d,2H), 6.83(d,2H), 3.82(d,2H), 3.77(s,3H), 3.73(s,3H), 3.42-3.01(m,6H), 1.81-1.16(m,16H), 0.85(m,3H).

(j) ^{1}H NMR (DMSO-d_6) δ 12.32(bs,1H), 7.43-6.8(m,11H), 3.78(s,3H), 3.73(s,3H), 3.65(s,2H), 3.35-3.01(m,6H), 1.77-1.16(m,16H), 0.87(m,3H).

(k) ^{1}H NMR ($CDCl_3$) δ 7.6-7.2(m,10H), 2.1(t,2H,J=7.4Hz), 2.5-2.3(m,7H), 1.8-1.6(m,2H), 1.5-1.2(m,18H), 0.9(quintet, 6H,J=5.1Hz).

(l) ^{1}H NMR (DMSO-d_6) δ 12.12(s,1H), 7.31(d,2H), 7.20(d,2H), 6.70(d,2H), 6.63(d,2H), 3.18(m,4H), 3.03(m,2H), 2.91(s,6H), 2.87(s,6H), 2.08(d,2H), 1.64-0.82(m,30H).

EXAMPLE 391

Preparation of cyclohexyl [5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]heptylcarbamate

To a solution of N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-1-heptanamine (0.87 g, 0.002 mol) and sodium bicarbonate (5%, 1 mL) in toluene (10 mL) at 0° was added, dropwise, a solution of cyclohexylchloroformate (0.32 g, 0.002 mol) in toluene (5 mL). The reaction mixture was allowed to warm to ambient temperature and stirred overnight. The solvent was removed under vacuum. The residue (1.0 g) was chromatographed with 7:3 hexane-ethyl acetate to give the title compound (0.61 g, 0.0011 mol) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 11.1(bs,1H), 7.7-7.2(m,10H), 4.6(bs,1H), 3.3(t,2H,J = 5.1Hz), 3.2(t,2H,J = 7.5Hz), 3.0-(t,2H,J = 5.2Hz), 1.9-1.2(m,26H), 0.9-0.8(m,3H).

EXAMPLE 401

Preparation of phenyl N-[5-(4,5-bis(1-methylethyl)-1H-imidazol-2-ylthio]pentyl]-N-heptylcarbamate

Part A. Employing the method of Example 118, Part B, but using phenyl chloroformate and triethylamine, phenyl, N-heptyl-N-(5-hydroxypentyl)carbamate was obtained as an oil (3.18 g, 0.00989 mol). ^{1}H NMR ($CDCl_3$) δ 7.40-7.06(m,5H), 3.68-3.63(m,2H), 3.42-3.27(m,4H), 2.08-1.95(bs,1H), 1.75-1.26(m,16H), 0.90-(t,3H).

Part B. Employing the method of Example 118, Part C, but using phenyl N-heptyl-N-(5-hydroxypentyl)-carbamate, phenyl N-(5-bromopentyl)-N-heptylcarbamate was isolated as an oil (3.8 g, 0.0099 mol). ^{1}H NMR ($CDCl_3$) δ 7.39-7.07(m,5H), 3.47-3.25(m,6H), 1.97-1.89(m,2H), 1.75-1.26(m,14H), 0.87(t,3H).

Part C. Employing the method of Example 118, Part D, but using phenyl N-(5-bromopentyl)-N-heptylcarbamate, the title compound was isolated as an oil (0.3 g, 0.000615 mol). ^{1}H NMR (DMSO-d_6) δ 11.07(s,1H), 7.35(m,2H), 7.18(t,1H), 7.05(d,2H), 3.31(m,2H), 3.20(m,2H), 2.95(m,3H), 2.8(m,1H), 1.67-1.06-(m,2H), 0.86(m,3H).

Additional carbamates, which are listed in Table 4, were prepared or could be prepared analogously according to the procedures of Examples 391 and 401.

Table 4

Ex. No.	R^1	R^2	R^3	R^4	X	Y	n	R^6	mp°C
391	C_6H_5	C_6H_5	H	C_6H_{11}	S	O	5	$(CH_2)_6CH_3$	oil
392	C_6H_5	C_6H_5	H	C_6H_5	S	O	5	$(CH_2)_6CH_3$	oil (a)
393	C_6H_5	C_6H_5	H	$CH_2CH(CH_3)_2$	S	O	5	$(CH_2)_6CH_3$	oil (b)
394	C_6H_5	C_6H_5	H	CH_2CH_3	S	O	5	$(CH_2)_6CH_3$	oil (c)
395	C_6H_5	C_6H_5	H	$(CH_2)_7CH_3$	S	O	5	$(CH_2)_6CH_3$	oil (d)
396	C_6H_5	C_6H_5	H	$4\text{-}FC_6H_4$	S	O	5	$(CH_2)_6CH_3$	oil (e)
397	C_6H_5	C_6H_5	H	$(CH_2)_2CH_3$	S	O	5	$(CH_2)_6CH_3$	oil (f)
398	C_6H_5	C_6H_5	H	$CH_2C_6H_5$	S	O	5	$(CH_2)_6CH_3$	oil (g)
399	$4\text{-}(CH_3)_2NC_6H_4$	$4\text{-}(CH_3)_2NC_6H_4$	H	C_6H_5	S	O	5	$(CH_2)_6CH_3$	oil (h)
400	$4\text{-}CH_3OC_6H_4$	$4\text{-}CH_3OC_6H_4$	H	C_6H_5	S	O	5	$(CH_2)_6CH_3$	oil (i)
401	$(CH_3)_2CH$	$(CH_3)_2CH$	H	C_6H_5	S	O	5	$(CH_2)_6CH_3$	oil

Table 4 (continued)

Ex. No.	R^1	R^2	R^3	R^4	X	Y	n	R^6	mp°C
402	n-C_3H_7	n-C_3H_7	H	n-C_3H_7	S	O	5	$(CH_2)_6CH_3$	
403	2-pyridinyl	2-pyridinyl	H	C_6H_{11}	O	O	5	$(CH_2)_6CH_3$	
404	3-pyridinyl	3-pyridinyl	H	2,4-di$CH_3OC_6H_3$	CH_2	O	5	$(CH_2)_6CH_3$	
405	4-pyridinyl	4-pyridinyl	H	CH_2-2,4,6-triFC_6H_2	NH	O	5	$(CH_2)_6CH_3$	
406	2-$CH_3OC_6H_4$	2-$CH_3OC_6H_4$	H	3-F-C_6H_4	S	H_2	5	$(CH_2)_6CH_3$	
407	3-$CH_3OC_6H_4$	3-$CH_3OC_6H_4$	H	$CH(CH_3)_2$	O	O	5	$(CH_2)_6CH_3$	
408	C_6H_{11}	C_6H_{11}	H	C_6H_5	CH_2	O	5	$(CH_2)_6CH_3$	
409	C_6H_5	4-$(CH_3)_2NC_6H_4$	H	$(CH_2)_7CH_3$	NH	O	5	$(CH_2)_6CH_3$	
410	2-furanyl	2-furanyl	H	2,6-diCl-C_6H_3	S	O	5	$(CH_2)_6CH_3$	
411	4-(t-C_4H_9)C_6H_4	4-(t-C_4H_9)C_6H_4	H	CH_3	O	H_2	5	$(CH_2)_6CH_3$	
412	2-thienyl	2-thienyl	H	(C_6H_4)(C_6H_5)	CH_2	O	5	$(CH_2)_6CH_3$	
413	4-HO-C_6H_4	4-HO-C_6H_4	CH_3	2,4-diFC_6H_3	NH	O	5	$(CH_2)_6CH_3$	
414	$(CH_3)_2CH$	$(CH_3)_2CH$	CH_3	C_6H_{11}	S	O	5	$(CH_2)_6CH_3$	
415	$C_6H_5CH_2$	$C_6H_5CH_2$	CH_3	C_6H_5	O	O	5	$(CH_2)_6CH_3$	
416	C_6H_4-2-OCH_2O-2'-C_6H_4		H	2,4-diFC_6H_3	CH_2	H_2	3	$(CH_2)_6CH_3$	
417	$C_6H_4OC_6H_4$		H	C_6H_{11}	NH	O	3	$(CH_2)_6CH_3$	
418	4-$CH_3OC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	C_6H_{11}	O	O	8	$(CH_2)_6CH_3$	
419	4-$CH_3OC_6H_4$	C_6H_{11}	H	CH_2-2,4-diFC_6H_3	CH_2	O	5	$(CH_2)_3CH_3$	
420	4-$CH_3OC_6H_4$	$(CH_3)_2CH$	H	CH_2-2,4-diFC_6H_3	NH	H_2	5	$(CH_2)_8CH_3$	

Table 4 (continued)

Ex. No.	R^1	R^2	R^3	R^4	X	Y	n	R^6	mp °C
421	4-$(CH_3)NC_6H_4$	C_6H_{11}	H	2,4-diFC_6H_3	S	0	5	CH_3	
422	4-$(CH_3)NC_6H_4$	$(CH_3)_2CH$	H	2,4-diFC_6H_3	0	0	5	C_6H_5	
423	C_6H_{11}	$(CH_3)_2CH$	H	CH_2-2,4-diFC_6H_3	CH_2	0	5	3-FC_6H_4	
424	C_6H_5	4-$CH_3OC_6H_4$	H	$(CH_2)_7CH_3$	NH	0	5	$(CH_2)_3CH_3$	
425	C_6H_5	4-$(CH_3)_2NC_6H_4$	H	$(CH_2)_7CH_3$	S	H_2	5	C_6H_5	
426	$(CH_3)_2CH$	$(CH_3)_2CH$	H	2,4-diFC_6H_3	S	0	5	$(CH_2)_6CH_3$	
427	4-$CH_3SC_6H_4$	4-$CH_3SC_6H_4$	H	2,4-diFC_6H_3	S	0	5	$(CH_2)_6CH_3$	
428	4-$CH_3SOC_6H_4$	4-$CH_3SOC_6H_4$	H	2,4-diFC_6H_3	NH	0	5	$(CH_2)_6CH_3$	
429	4-$CH_3SO_2C_6H_4$	4-$CH_3SO_2C_6H_4$	H	2,4-diFC_6H_3	CH_2	0	5	$(CH_2)_6CH_3$	
430	C_6H_5	4-$CH_3SC_6H_4$	C_6H_5	2,4-diFC_6H_3	S	0	5	$(CH_2)_6CH_3$	
431	C_6H_5	4-$CH_3SOC_6H_4$	CH_2CH_3	2,4-diFC_6H_3	NH	0	5	$(CH_2)_6CH_3$	
432	C_6H_5	4-$CH_3SO_2C_6H_4$	$CH_2C_6H_5$	2,4-diFC_6H_3	CH_2	0	5	$(CH_2)_6CH_3$	
433	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	CH_3	n-C_3H_7	S	0	5	$(CH_2)_6CH_3$	
434	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	C_6H_{11}	S	H_2	5	$(CH_2)_6CH_3$	
435	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	$CH(CH_3)_2$	S	0	5	$(CH_2)_6CH_3$	
436	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	C_6H_5	SO	0	5	$(CH_2)_6CH_3$	
437	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	2,4-diFC_6H_3	S	0	3	$(CH_2)_6CH_3$	
438	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	C_6H_{11}	S	0	8	$(CH_2)_6CH_3$	
439	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	$(CH_2)_7CH_3$	SO_2	0	5	C_6H_5	

Table 4 (continued

Ex. No.	R^1	R^2	R^3	R^4	X	Y	n	R^6	mp °C
440	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	n-C_3H_7	S	0	5	$(CH_2)_6CH_3$	
441	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	C_6H_{11}	S	H_2	5	$(CH_2)_6CH_3$	
442	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	CH_3	$CH(CH_3)_2$	S	0	5	$(CH_2)_6CH_3$	
443	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	C_6H_5	SO	0	5	$(CH_2)_6CH_3$	
444	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	2,4-diFC_6H_3	S	0	3	$(CH_2)_6CH_3$	
445	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	C_6H_{11}	SO_2	0	8	$(CH_2)_6CH_3$	
446	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	$(CH_2)_7CH_3$	S	S	5	C_6H_5	

Footnotes To Table 4

(a) ^{1}H NMR ($CDCl_3$) δ 10.6(s,1H), 7.7-7.0(m,15H), 3.4(q,4H,J=4.7Hz),2.9(t,2H,J=5.8Hz), 1.8-1.2(m,16H), 0.95-0.75(m,3H).

(b) ^{1}H NMR ($CDCl_3$) δ 10.9(s,1H), 7.75-7.1(m,10H), 3.75(d,2H,J=6.3Hz), 3.3(t,2H,J=6.0Hz), 3.15(t,2H,J=7.5Hz), 3.0(t,2H,J=6.2Hz), 2.0-1.2(m,17H), 0.9(t,9H,J=3.2Hz).

(c) ^{1}H NMR ($CDCl_3$) δ 10.9(s,1H), 7.75-7.1(m,10H), 4.0(d,2H,J=6.8Hz), 3.4-2.95(m,6H), 1.9-1.1(m,19H), 1.0-0.8(m,3H).

(d) ^{1}H NMR ($CDCl_3$) δ 10.7(s,1H), 7.7-7.2(m,10H), 4.1 to 3.9(m,2H), 3.4-2.9(m,6H), 1.8-1.2(m,28H), 0.9-0.8(m,6H).

(e) ^{1}H NMR ($CDCl_3$) δ 10.4(s,1H), 7.7-6.8(m,14H), 3.5-2.9(m,6H), 1.9-1.1(m,16H), 1.0-0.8(m,3H).

(f) ^{1}H NMR ($CDCl_3$) δ 10.9(s,1H), 7.75-7.1(m,10H), 4.0(q,2H,J=6.9Hz), 3.3(t,2H,J=9.5Hz), 3.2(t,2H,J=7.5Hz), 3.0(t,2H,J=7.8Hz), 1.8-1.1(m,18H), 0.9(t,3H,J=7.2Hz).

(g) ^{1}H NMR ($CDCl_3$) δ 10.5(s,1H), 7.7-7.2(m,15H), 5.05(s,2H), 3.3(q,2H,J=5.7Hz), 3.2(t,2H,J=7.4Hz), 3.0(q,2H,J=5.4Hz), 1.8-1.1(m,16H), 0.9(t,3H,J=6.4Hz).

(h) ^{1}H NMR ($CDCl_3$) δ 10.0-9.8(bs,1H), 7.57-7.03(m,9H), 6.63(m,4H), 3.43-3.26(m,4H), 3.09-2.86(bs,14H), 1.81-1.25(m,16H), 0.89(t,3H).

(i) ^{1}H NMR (DMSO-d_6) δ 12.34(s,1H), 7.39-7.22(m,6H), 7.19(t,1H), 7.06(d,2H), 6.94(d,2H), 6.84(d,2H), 3.77(s,3H), 3.72(s,3H), 3.40-3.20(m,4H), 3.09(m,2H), 1.75-1.17(m,16H), 0.84(m,3H).

Table 5

Ex. No.	R^1	R^2	R^3	X	A	Y	Z	R^6
447	C_6H_5	C_6H_5	H	S	$CH_2CH(CH_3)(CH_2)_3$	O	NH-2,4-diFC_6H_3	$(CH_2)_6CH_3$
448	C_6H_5	C_6H_5	H	CH_2	$(CH_2)_3CH(CH_3)CH_2$	S	NH-2,4-diFC_6H_3	$(CH_2)_3CH_3$
449	C_6H_5	C_6H_5	H	NH	$(CH_2)_3C(CH_3)_2CH_2$	H_2	NH-2,4-diFC_6H_3	$(CH_2)_8CH_3$
450	C_6H_5	C_6H_5	H	O	$(CH_2)CH(C_5H_{11})(CH_2)_2$	O	$CH_2CH(CH_3)_2$	C_6H_5
451	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	CH_3	S	$CH(CH_3)(CH_2)_4$	S	$CH_2CH(CH_3)_2$	2,4-diFC_6H_3
452	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	CH_2	$CH_2CH=CH(CH_2)_2$	H_2	$CH_2CH(CH_3)_2$	$(CH_2)_6CH_3$
453	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	CH_2CH_3	NH	$(CH_2)_3CH=CH(CH_2)_2$	O	$O(CH_2)_7CH_3$	$(CH_2)_3CH_3$
454	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	$CH_2C_6H_5$	O	$CH_2C\equiv C(CH_2)_2$	S	$O(CH_2)_7CH_3$	CH_3
455	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	C_6H_5	S	$(CH_2)_3C\equiv C(CH_2)_2$	H_2	$O(CH_2)_7CH_3$	C_6H_5
456	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	CH_2	$CH_2CH(CH_3)(CH_2)_3$	O	$NHCH(CH_3)_2$	$(CH_2)_6CH_3$
457	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	NH	$(CH_2)_3CH(CH_3)CH_2$	S	$NHCH(CH_3)_2$	$(CH_2)_3CH_3$

Table 5 (continued

Ex. No.	R1	R2	R3	X	A	Y	Z	R6
458	4-CH3OC6H4	4-CH3OC6H4	H	O	(CH2)3CH(CH3)2CH2	H2	NHCH(CH3)2	(CH2)8CH3
459	(CH3)2CH	(CH3)2CH	H	S	(CH2)2CH(C5H11)(CH2)2	O	(CH2)7CH3	C6H5
460	(CH3)2CH	(CH3)2CH	CH3	CH2	CH(CH3)(CH2)4	S	(CH2)7CH3	2,4-diFC6H3
461	(CH3)2CH	(CH3)2CH	H	NH	CH2CH=CH(CH2)2	H2	(CH2)7CH3	(CH2)6CH3
462	(CH3)2CH	(CH3)2CH	H	O	(CH2)3CH=CH(CH2)2	O	OC6H5	(CH2)3CH3
463	C6H11	C6H11	H	S	CH2C≡C(CH2)2	S	OC6H5	CH3
464	C6H11	C6H11	C6H5	CH2	(CH2)3C≡C(CH2)2	H2	OC6H5	C6H5
465	C6H11	C6H11	H	NH	CH2CH(CH3)(CH2)3	O	NH(CH2)7CH3	(CH2)6CH3
466	C6H11	C6H11	H	O	(CH2)3CH(CH3)CH2	S	NH(CH2)7CH3	(CH2)3CH3
467	C6H5	4-CH3OC6H4	H	S	(CH2)3C(CH3)2CH2	H2	NH(CH2)7CH3	(CH2)8CH3
468	C6H5	4-CH3OC6H4	H	CH2	(CH2)2CH(C5H11)(CH2)2	O	CH2C6H5	C6H5
469	C6H5	4-CH3OC6H4	CH3	NH	CH(CH3)(CH2)4	S	C6H5	2,4-diFC6H3
470	C6H5	4-CH3OC6H4	H	O	CH2CH=CH(CH2)2	H2	CH2C6H5	(CH2)6CH3
471	C6H5	4-(CH3)2NC6H4	H	S	(CH2)3CH=CH(CH2)2	O	OCH(CH3)2	(CH2)3CH3
472	C6H5	4-(CH3)2NC6H4	H	CH2	CH2C≡C(CH2)2	S	OCH(CH3)2	CH3
473	C6H5	4-(CH3)2NC6H4	C6H5	NH	(CH2)3C≡C(CH2)2	H2	OCH(CH3)2	C6H5
474	4-(CH3)2NC6H4	4-(CH3)2NC6H4	H	S	CH2CH(CH3)(CH2)3	O	CH2CH(CH3)2	(CH2)3CH3
475	4-(CH3)2NC6H4	4-(CH3)2NC6H4	H	S	(CH2)3CH(CH3)CH2	O	O(CH2)7CH3	(CH2)6CH3
476	4-(CH3)2NC6H4	4-(CH3)2NC6H4	H	S	(CH2)3C(CH3)2CH2	O	NH-2,4-diFC6H3	(CH2)6CH3

Table 5 (continued

Ex. No.	R^1	R^2	R^3	X	A	Y	Z	R^6
477	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	SO	$(CH_2)_2CH(C_5H_{11})(CH_2)_2$	O	NH-2,4-diFC_6H_3	$(CH_2)_8CH_3$
478	4-$(CH_3)_2NC_6H_4$	4-$(CH_3)_2NC_6H_4$	H	SO_2	$CH(CH_3)(CH_2)_4$	O	$NH(CH_2)_2CH_3$	$(CH_2)_6CH_3$
479	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4C_6H_4$	H	S	$CH_2CH=CH(CH_2)_2$	O	CH$_2$-2,4-diFC_6H_3	$(CH_2)_3CH_3$
480	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	S	$(CH_2)_3CH=CH(CH_2)_2$	O	O-2,4-diFC_6H_3	$(CH_2)_3CH_3$
481	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	S	$CH_2C\equiv C(CH_2)_2$	O	CH_2-$CH(CH_3)_2$	$(CH_2)_6CH_3$
482	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	S	$(CH_2)_3C\equiv C(CH_2)_2$	O	CH_2CH_3	$(CH_2)_6CH_3$

Utility

The compounds of the present invention are inhibitors of the enzyme acyl-CoA: cholesterol acyltransferase and are thus effective in inhibiting esterification and transport of cholesterol across the intestinal wall.

A. Asssay of the Inhibition of Acyl-CoA: Cholesterol Acyltransferase (ACAT) in Hepatic Microsomes

The ability of the compounds to inhibit ACAT, the enzyme responsible for the intracellular synthesis of cholesteryl esters, was tested as follows. Male Sprague Dawley rats weighing 150-300 g, were fed rat chow ad libitum. The animals were fasted for twenty-four hours prior to being sacrificed by decapitation. The livers were perfused in situ with 50 ml of cold 0.25 M sucrose, excised, and homogenized in three volumes of 0.1 M phosphate buffer, pH 7.4, that contained 0.5 mM EDTA (ethylenediaminetetraacetic acid), 1.0 mM glutathione, 0.25 M sucrose and 20 mM leupeptin. Microsomes were obtained by differential centrifugation; the supernatant from an initial spin at 15,000 x g for 15 minutes was centrifuged at 105,000 x g for 1 hour to pellet the microsomes. The microsomes were suspended in homogenization buffer, reisolated by centrifugation, and stored at -70 °C. Microsomes were used within one month of preparation.

The control assay in a final volume of 200 µl consisted of 200 µg of microsomal protein, 75 µm ^{14}C-oleoyl-CoA (10,000 dpm/nmol) in 0.1 M phosphate, pH 7.4, that contained 1 mM glutathione. Compounds were added in 5-10 µl of DMSO (dimethyl sulfoxide) and addtional controls were run with DMSO only. All components, except the oleoyl-CoA, were preincubated for 15 min. at 37 °C prior to the initiation of the reaction by the addition of oleoyl-CoA. The assay was terminated after 10 min by the addition of 500 µl of hexane: isopropanol (3:2, v/v). 20,000 dpm of ^{3}H-cholesteryl oleate and 10 µg of unlabeled cholesteryl oleate and oleic acid were added as an internal standard and carriers, respectively. After allowing 10 min. for lipid extraction, the samples were centrifuged at 1,000 x g for 10 min. to separate the solvent layers. 200 µl of the top (hexane) layer containing the neutral lipids was spotted onto a Baker SI250-Pa silica gel TLC plate and the plate developed using a hexane: diethyl ether: acetic acid (170:30:1 v/v/v) mobile phase. The lipids were visualized by their interaction with iodine vapor and the cholesteryl ester spot was scraped into a scintillation vial and counted. The specific activity of ACAT in the control incubation averaged 260 pmol/min/mg microsomal protein. The inhibition of ACAT activity by the compounds is shown in Table 6; the data are expressed as the concentration at which ACAT activity is inhibited by 50% (IC_{50}).

B. Assay of the Inhibition of Cholesterol Esterification in Mammalian Cells

The esterification of cholesterol was determined in the murine macrophage-like cell line J774.A1. Cells were seeded in 35 mm wells at a density of 300,000 cells per well in 2 mls of Dulbecco's Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS). Cells were incubated at 37 °C in an atmosphere of 5% CO_2 and 93% humidity. After 24 hours the media was changed to 0.68 mls 10% FBS-DMEM containing 34 µg of acetylated human low density lipoprotein (ac-LDL) to increase the intracellular concentration of cholesterol and promote esterification. At 41 hours, various inhibitors were added to the cells in DMSO (10 µl/ml maximum). At 43 hours, the cells were pulsed with 0.1 mM ^{14}C-oleic acid (10,000 dpm/nmol) complexed with BSA (bovine serum albumin) to follow cholesterol ester formation. The experiment was terminated at 45 hours by washing the monolayers 3 times with 3 ml of Tris-buffered saline at 4 °C. The lipids were extracted by incubating the monolayers with 1.5 ml of hexane: isopropanol (3:2, v/v) for 30 min. under gentle agitation. During this period, 10,000 dpm ^{3}H-cholesteryl linoleate and 10 µg of cholesteryl oleate were added as an internal standard and carrier respectively. The organic solvent was removed and the cells were washed with an additional 1.0 ml of hexane: isopropanol which was combined with the original extract. The cells were allowed to dry overnight, digested with 1.5 ml of 0.2 N sodium hydroxide for 1 hour and an aliquot of the solubilized protein used for protein determination using the Lowry method. The organic extract was taken to dryness, the residue resuspended in 100 µl of chloroform and the lipids separated on silica gel impregnated glass fiber plates using a hexane: diethylether: acetic acid (170:30:1, v/v/v) solvent system. Individual lipids were visualized with iodine and the cholesteryl ester spot cut out and transferred to scintillation vials to determine the amount of radioactivity. The conversion of oleic acid to cholesteryl ester in control averaged 0.54 mmol/hour/mg protein and was increased upon the addition of ac-LDL to about 10.69 ± 0.69 mmol/hour/mg protein. The inhibition of esterification by the compounds is shown in Table 7; the data are expressed as the concentration at which ACAT activity is inhibited by 50% (IC_{50}). It should be noted that many of the intermediates had inhibitory activity in the in vitro ACAT assay and in the macrophage assay. For example, N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)-pentyl]-1-heptanaminehydrochloride had IC_{50}'s of 100 nM and 6 µm in the in vitro ACAT and macrophage assay, respectively.

C. Assay of Antihypercholesterolemic Activity in Cholesterol-fed Hamsters

Inhibition of ACAT activity in the gut reduces the absorption of cholesterol in cholesterol-fed animals. Hamsters weighing approximately 100 g, were maintained on a diet supplemented with 0.8% cholesterol. The treatment group received 1-100 mg/kg/day, p.o., of the test compound dissolved in 500 µl of corn oil for a period of two weeks. The control group were pair-fed to the treatment group and were dosed with 500 µl of the corn oil vehicle. At sacrifice, the hamsters were anesthetized with CO_2 and exsanguinated via cardiac puncture. Total serum cholesterol was determined on a Du Pont aca® IV. The data were expressed in terms of mg cholesterol per 100 ml of serum (mg %). The antihypercholesterolemic activity of the compound of Example 1 is shown in Table 8.

Table 6

Inhibition of In Vitro Hepatic ACAT Activity by Various Compounds

Compound of Example	In Vitro ACAT IC_{50} (nM)
1	13
2	23
3	8
4	60
5	12
6	3,600
7	41
8	10
9	930
53	17
64	30
71	16
85	60
94	10
97	25
105	20
107	1,000
110	60
114	40
118	170
122	80
160	490
186	2,850
188	20
189	70
190	30
191	400
192	70

Table 6 (continued)

Compound of Example	In Vitro ACAT IC_{50} (nM)
193	60
195	40
196	300
197	119
198	40
199	20
200	710
201	200
204	500
206	40
207	9
208	20
209	1,400
212	60
267	58
269	8
272	16
289	30
290	140
291	130
329	3,500
330	280
331	25
332	3
333	30
334	160
335	30
338	30
339	700
340	200

Table 6 (continued)

Compound of Example	In Vitro ACAT IC_{50} (nM)
341	605
342	250
343	300
344	240
392	20
393	35
394	33
395	500
396	10
397	40
398	9
399	120

Table 7

Inhibition of Cholesterol Esterification in Macrophage by Various Compounds

Compound of Example	Cholesterol Esterification IC_{50} (μM)
1	1.0
2	0.8
3	17.5
4	4.6
5	2.5
6	3.8
7	7.5
8	0.5

Table 7 (continued)

Inhibition of Cholesterol Esterification in Macrophage by Various Compounds

Compound of Example	Cholesterol Esterification IC_{50} (μM)
9	11.2
53	0.4
64	0.6
71	1.9
85	3.1
94	0.1
97	0.7
105	0.3
107	2.3
110	0.9
114	3.5
118	0.1
122	0.3
160	1.6
186	6.2
188	0.9
189	2.2
191	2.4
192	2.0
193	2.7
195	0.4
196	1.4
197	0.1
199	0.6
206	0.4
207	0.6

Table 7 (continued)

Inhibition of Cholesterol Esterification in Macrophage by Various Compounds

Compound of Example	Cholesterol Esterification IC_{50} (μM)
209	4.8
212	1.7
267	6.1
269	1.2
272	3.5
289	2.5
290	1.2
291	0.9
329	3.4
330	4.4
331	0.2
332	0.1
333	1.6
334	1.1
338	0.3
339	0.2
392	0.4
393	0.5
394	0.5
395	3.9
396	0.6
397	0.8
398	1.3

Table 8

Dose Response Evaluation of Example 1 in Hypercholesterolemic Hamsters			
Dose (mg/kg/day)	Serum Cholesterol (mg %)[a]		Decrease (%)
	Control	Treated	
1	400 ± 25	295 ± 12	26
3	381 ± 17	279 ± 16	27
10	371 ± 7	201 ± 12	46
30	368 ± 15	197 ± 11	46
100	400 ± 17	162 ± 8	60

a) Values are the mean ± SEM, n=9-10 per group

Dosage Forms:

The compounds of the present invention can be administered orally using any pharmaceutically acceptable dosage form known in the art for such administration. The active ingredient can be supplied in solid dosage forms such as dry powders, granules, tablets or capsules, or in liquid dosage forms, such as syrups or aqueous suspensions. The active ingredient can be administered alone, but is generally administered with a pharmaceutical carrier. A valuable treatise with respect to pharmaceutical dosage forms is Remington's Pharmaceutical Sciences, 16th Edition, 1980.

In the therapeutic use of intestinal ACAT inhibitors, the compounds utilized are administered to the patient at dosage levels of 1 to 28 g per day. For a normal male adult human of approximately 70 kg of body weight, this translates into a dosage of 14 to 400 mg per kilogram body weight per day. The dosage administered will, of course, vary depending upon known factors such as the age, health, and weight of the recipient; nature and extent of symptoms, kind of concurrent treatment, frequency of treatment, and the effect desired. Useful pharmaceutical dosage forms for administration of the compounds of this invention can be illustrated as follows:

Tablets

Tablets are prepared by conventional procedures so that the dosage unit is 500 milligrams of active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose and 10 milligrams of magnesium stearate.

Capsules

Capsules are prepared by conventional procedures so that the dosage unit is 500 milligrams of active ingredient, 100 milligrams of cellulose and 10 milligrams of magnesium stearate.

Syrup

	Wt. %
Active Ingredient	10
Liquid Sugar	50
Sorbitol	20
Glycerine	5
Flavor, Colorant and Preservative	as required
Water	as required

The final volume is brought up to 100% by the addition of distilled water.

Aqueous Suspension

	Wt. %
Active Ingredient	10
Sodium Saccharin	0.01
Keltrol® (Food Grade Xanthan Gum)	0.2
Liquid Sugar	5
Flavor, Colorant and Preservative	as required
Water	as required

Xanthan gum is slowly added into distilled water before adding the active ingredient and the rest of the formulation ingredients. The final suspension is passed through a homogenizer to assure the elegance of the final products.

Resuspendible Powder

	Wt. %
Active Ingredient	50.0
Lactose	35.0
Sugar	10.0
Acacia	4.7
Sodium Carboxylmethylcellulose	0.3

Each ingredient is finely pulverized and then uniformly mixed together. Alternatively, the powder can be prepared as a suspension and then spray dried.

Semi-Solid Gel

	Wt. %
Active Ingredient	10
Sodium Saccharin	0.02
Gelatin	2
Colorant, Flavor and Preservative	as required
Water	as required

Gelatin is prepared in hot water. The finely pulverized active ingredient is suspended in the gelatin solution and then the rest of the ingredients are mixed in. The suspension is filled into a suitable packaging container and cooled down to form the gel.

Semi-Solid Paste

	Wt. %
Active Ingredient	10
Gelcarin® (Carrageenin gum)	1
Sodium Saccharin	0.01
Colorant, Flavor and Preservative	as required
Water	as required

Gelcarin® is dissolved in hot water (around 80 °C) and then the fine-powder active ingredient is suspended in this solution. Sodium saccharin and the rest of the formulation ingredients are added to the suspension while it is still warm. The suspension is homogenized and then filled into suitable containers.

Emulsifiable Paste

	Wt. %
Active Ingredient	30
Tween® 80 and Span® 80	6
Keltrol®	0.5
Mineral Oil	63.5

All the ingredients are carefully mixed together to make a homogenous paste.

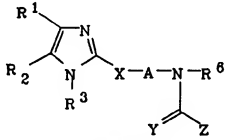
The term "consisting essentially of" in the present disclosure is intended to have its customary meaning; namely, that all specified materials and conditions are very important in practicing the invention but that unspecified materials and conditions are not excluded so long as they do not prevent the benefits of the invention from being realized.

The foregoing disclosure includes all the information deemed essential to enable those of skill in the art to practice the claimed invention. The cited publications and applications may provide further useful information.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, GR, IT, LI, LU, NL, SE

1. A compound of the formula

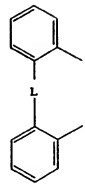


Formula (I)

wherein

R^1 and R^2 are selected independently from H, C_1-C_8 alkyl, provided that when R^1 is H, then R^2 cannot be H and when R^1 is C_1-C_8 alkyl, then R^2 cannot be C_1-C_8 alkyl, C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_7-C_{14} araalkyl, 2-, 3- or 4-pyridinyl, 2-thienyl, 2-furanyl, phenyl optionally substituted with 1 to 3 groups selected from F, Cl, Br, OH, C_1-C_4 alkoxy, C_1-C_4 alkyl, C_3-C_6 branched alkyl, $CH_3S(O)_n$, NO_2, CF_3, or NR^7R^8; or

R^1 and R^2 can also be taken together as



where L is O, $O(CH_2)_{m+1}O$, or $(CH_2)_m$ where m is 0-4;

R^3 is H, C_1-C_6 alkyl, allyl, benzyl, or phenyl optionally substituted with F, Cl, CH_3, CH_3O, or CF_3;

R^4 is straight chain C_1-C_8 alkyl optionally substituted with F; C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_7-C_{14} araalkyl where the aryl group is optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl or alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8, or $NCOR^7$; C_3-C_6 alkenyl or alkynyl, C_1-C_3 perfluoroalkyl, phenyl optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl,C_1-C_4 alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8 or $NCOR^7$; pentafluorophenyl, benzyl optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl or alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8, or $NCOR^7$; 2-, 3- or 4-pyridinyl, pyrimidinyl, or biphenyl;

R^5 is H, C_1-C_6 alkyl, or benzyl;

R^6 is H, C_1-C_8 alkyl, C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, C_3-C_8 alkenyl or alkynyl, phenyl optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl or alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8, or $NCOR^7$; pentafluorophenyl, benzyl optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl or alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8, or $NCOR^7$;

R^7 and R^8 are selected independently from H or C_1-C_4 alkyl;

X is $S(O)_r$, O, NR^5, CH_2;

A is C_2-C_{10} alkyl, C_3-C_{10} branched alkyl, C_3-C_{10} alkenyl, or C_3-C_{10} alkynyl;

Y is O, S, H_2;

Z is NHR^4, OR^4, or R^4;

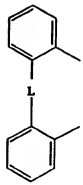
r is 0-2,

or a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1 wherein

R^1 and R^2 are selected independently from C_1-C_8 alkyl, provided that when R^1 is C_1-C_8 alkyl, then R^2 cannot be C_1-C_8 alkyl, C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_7-C_{14} araalkyl, 2-, 3-, or 4-pyridinyl, 2-thienyl, 2-furanyl, phenyl optionally substituted with 1 to 2 groups selected from F, Cl, Br, OH, C_1-C_4 alkoxy, C_1-C_4 alkyl, C_3-C_8 branched alkyl, $CH_3S(O)_r$, NO_2, CF_3, or NR^7R^8; or

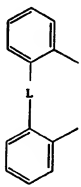
R^1 and R^2 can also be taken together as



where L is O, $O(CH_2)_{m+1}O$, or $(CH_2)_m$ where m is 0-4.

3. A compound of Claim 2 wherein
   - R^3 is H, CH_3, phenyl;
   - R^6 is H, C_1-C_8 alkyl, C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, phenyl optionally substituted with 1 to 3 groups selected from CH_3, CH_3O, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, or di(C_1-C_4)-alkylamino; or benzyl optionally substituted with 1 to 3 groups selected from CH_3, CH_3O, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, or di(C_1-C_4)alkylamino;
   - X is $S(O)_r$, CH_2;
   - A is C_2-C_{10} alkyl, C_4-C_9 branched alkyl.

4. A compound of Claim 3, wherein R^1 and R^2 are selected independently from C_1-C_8 alkyl, C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_7-C_{14} araalkyl, 2-, 3-, or 4-pyridinyl, 2-thienyl, or phenyl optionally substituted with 1 to 2 groups selected from F, Br, Cl, C_1-C_4 alkyl, C_3-C_8 branched alkyl, CH_3O, $CH_3S(O)_t$, NO_2, CF_3, or di(C_1-C_4)alkylamino; or
   - R^1 and R^2 can also be taken together as

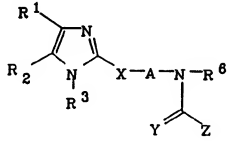


   where L is O or OCH_2O;
   - R^3 is H;
   - R^4 is C_1-C_8 alkyl, C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_7-C_{14} araalkyl, phenyl substituted with 1 to 3 groups selected from CH_3, F, Cl, CH_3O, CN; or benzyl optionally substituted with 1 to 3 groups selected from CH_3, CH_3O, F, Cl, or CN;
   - R^6 is C_1-C_8 alkyl or phenyl optionally substituted with 1 to 3 groups selected from CH_3, CH_3O, F, Cl, or CN;
   - A is C_4-C_9 alkyl;
   - X is $S(O)_t$;
   - Y is O, H_2.

5. Compounds of claims 1 to 4, selected from N'-(2,4-difluorophenyl)-N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptylurea;
N'-(2,4-difluorophenyl)-N-[8-(4,5-diphenyl-1H-imidazol-2-ylthio)octyl]-N-heptylurea;
N-butyl-N'-(2,4-dlfluorophenyl)-N-[8-(4,5-diphenyl-1H-imidazol-2-ylthio)octyl]urea;
N'-(2,4-dimethoxyphenyl)-N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptylurea;
N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptyl-N'-methylurea;
N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptyl-N'-propylurea;
N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N'-(3-fluorophenyl)-N-heptylurea;
N'-(2,4-difluorophenyl)-N-[5-[(4,5-diphenyl-1H-imidazol-2-yl)sulfonyl])pentyl]-N-heptylurea;
N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptyl-N'-(1-methylethyl)urea;
N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-2,4-difluoro-N-heptylbenzeneacetamide;
N'-cyclohexyl-N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptylurea;
N'-(2,4-difluorophenyl)-N-[5-[(4,5-diphenyl-1H-imidazol-2-yl)sulfinyl]pentyl]-N-heptylurea;
N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptylbutanamide;
N-[5-[4,5-bis(1-methylethyl)-1H-imidazol-2-ylthio]pentyl]-N'-(2,4-difluorophenyl)-N-heptylurea;
N-[5-[4,5-bis(1-methylethyl)-1H-imidazol-2-ylthio]pentyl]-N-heptylcyclohexaneacetamide;
N-[5-[4,5-bis(2-methoxyphenyl)-1H-imidazol-2-ylthio]pentyl]-N'-(2,4-difluorophenyl)-N-heptylurea;
phenyl [5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]heptylcarbamate;
N-[5-[4,5-bis[4-(dimethylamino)phenyl]-1H-imidazol-2-ylthio]pentyl]-N'-(2,4-difluorophenyl)-N-heptylurea;
N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N'-octyl-N-phenylurea;
N-[5-[4,5-bis(4-methoxyphenyl)-1H-imidazol-2-ylthio]pentyl]-2,4-difluoro-N-heptylbenzeneacetamide;
phenyl [5-[4,5-bis(4-(dimethylamino)phenyl)-1H-imidazol-2-ylthio]pentyl]heptylcarbamate;
and N-[5-(4,5-dicyclohexyl-1H-imidazol-2-ylthio)pentyl]-N'-(2,4-difluorophenyl)-N-heptylurea.

6. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claims 1 to 5 and a pharmaceutically acceptable carrier.

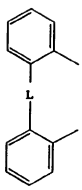
7. A process for preparing a compound of Formula (I):



wherein

R^1 and R^2 are selected independently from H, C_1-C_8 alkyl, provided that when R^1 is H, then R^2 cannot be H and when R^1 is C_1-C_8 alkyl, then R^2 cannot be C_1-C_8 alkyl, C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_7-C_{14} araalkyl, 2-, 3- or 4-pyridinyl, 2-thienyl, 2-furanyl, phenyl optionally substituted with 1 to 3 groups selected from F, Cl, Br, OH, C_1-C_4 alkoxy, C_1-C_4 alkyl, C_3-C_8 branched alkyl, $CH_3S(O)_n$, NO_2, CF_3, or NR^7R^8; or

R^1 and R^2 can also be taken together as



where L is O, $O(CH_2)_{m+1}O$, or $(CH_2)_m$ where m is 0-4;

R^3 is H, C_1-C_6 alkyl, allyl, benzyl, or phenyl optionally substituted with F, Cl, CH_3, CH_3O, or CF_3;

R^4 is straight chain C_1-C_8 alkyl optionally substituted with F; C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_7-C_{14} araalkyl where the aryl group is optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl or alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8, or $NCOR^7$; C_3-C_6 alkenyl or alkynyl, C_1-C_3 perfluoroalkyl, phenyl optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl,C_1-C_4 alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8 or $NCOR^7$; pentafluorophenyl, benzyl optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl or alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8, or $NCOR^7$; 2-, 3- or 4-pyridinyl, pyrimidinyl, or biphenyl;

R^5 is H, C_1-C_6 alkyl, or benzyl;

R^6 is H, C_1-C_8 alkyl, C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, C_3-C_8 alkenyl or alkynyl, phenyl optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl or alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8, or $NCOR^7$; pentafluorophenyl, benzyl optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl or alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8, or $NCOR^7$;

R^7 and R^8 are selected independently from H or C_1-C_4 alkyl;

X is $S(O)_r$, O, NR^5, CH_2;

A is C_2-C_{10} alkyl, C_3-C_{10} branched alkyl, C_3-C_{10} alkenyl, or C_3-C_{10} alkynyl;

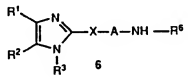
Y is O, S, H_2;

Z is NHR^4, OR^4, or R^4;

r is 0-2,

or a pharmaceutically acceptable salt thereof, comprising the steps of:

reacting a compound of the formula



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where R^1, R^2, X, A, and R^6, are as defined above, and R^3 is as defined above, or a suitable protecting group, such as a silyl or a trityl group,

with:

i) an isocyanate of the formula, R^4-N=C=O, where R^4 is as defined above, to yield a compound of Formula (I) above, where Y is O, and Z is NHR^4; or

ii) an isothiocyanate of the formula, R^4-N=C=S, where R^4 is as defined above, to yield a compound of Formula (I) above, where Y is S, and Z is NHR^4; or

iii) a chloroformate of the formula,

where R^4 is as defined above, to yield a compound of Formula (I) above where Y is O and Z is OR^4; or

iv) an acid chloride of the formula,

or other activated carboxylic acid, where R^4 is as defined above, to yield a compound of Formula (I) above where Y is O and Z is R^4.

8. A process of Claim 7 , further comprising removing any protecting group on R^3, to yield a compound of Formula (I), where R^3 is H.

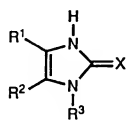
9. A process of Claim 7 , further comprising reacting a compound of Formula (I) where Y is O with Lawesson's reagent or diphosphorous pentasulfide to yield a compound of Formula (I) where Y is S.

10. A process of Claim 7 , further comprising reacting a compound of Formula (I) where Y is O with a reducing agent such as lithium aluminum hydride or sodium borohydride, to yield a compound of Formula (I) where Y is H_2.

11. A process of Claim 7 , further comprising reacting a compound of Formula (I) where X is S with a suitable oxidizing agent to yield either the sulfoxide, SO, where r is 1, or the sulfone, SO_2, where r is 2.

12. A process of Claim 7 , further comprising reacting a compound of Formula (I) where R^3 is H with a suitable alkylating agent such as an alkyl halide, to yield a compound of Formula (I) where R^3 is C_1-C_6 alkyl, allyl, or benzyl.

13. A process comprising the steps of alkylating a compound of the formula,

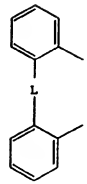


wherein

R^1 and R^2 are selected independently from H, C_1-C_8 alkyl, provided that when R^1 is H, then R^2 cannot be H and when R^1 is C_1-C_8 alkyl, then R^2 cannot be C_1-C_8 alkyl, C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_7-C_{14} araalkyl, 2-, 3- or 4-pyridinyl, 2-thienyl, 2-furanyl, phenyl optionally substituted with 1 to 3 groups selected from F, Cl, Br, OH, C_1-C_4 alkoxy, C_1-C_4 alkyl, C_3-C_8 branched alkyl, $CH_3S(O)_r$, NO_2,

CF_3, or NR^7R^8; or

R^1 and R^2 can also be taken together as

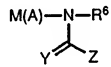


where L is O, $O(CH_2)_{m+1}O$, or $(CH_2)_m$ where m is 0-4;

R^3 is H, C_1-C_6 alkyl, allyl, benzyl, or phenyl optionally substituted with F, Cl, CH_3, CH_3O, CF_3, or an appropriate protecting group, such as a silyl or trityl group, and

X is O or S,

with a compound of the formula,



where

M is halide or tosylate,

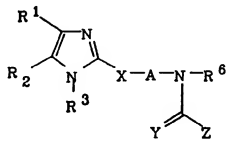
A is C_2-C_{10} alkyl, C_3-C_{10} branched alkyl, C_3-C_{10} alkenyl, or C_3-C_{10} alkynyl;

R^6 is H, C_1-C_8 alkyl, C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, C_3-C_8 alkenyl or alkynyl, phenyl optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl or alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8, or $NCOR^7$; pentafluorophenyl, benzyl optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl or alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8, or $NCOR^7$;

Y is O, S, or H_2, and

Z is NHR^4, OR^4, or R^4,

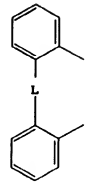
to yield a compound of Formula (I):



wherein

R^1 and R^2 are selected independently from H, C_1-C_8 alkyl, C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_7-C_{14} araalkyl, 2-, 3- or 4-pyridinyl, 2-thienyl, 2-furanyl, phenyl optionally substituted with 1 to 3 groups selected from F, Cl, Br, OH, C_1-C_4 alkoxy, C_1-C_4 alkyl, C_3-C_8 branched alkyl, $CH_3S(O)_y$, NO_2, CF_3, or NR^7R^8; or

R^1 and R^2 can also be taken together as



where L is O, $O(CH_2)_{m+1}O$, or $(CH_2)_m$ where m is 0-4;

R^3 is H, C_1-C_6 alkyl, allyl, benzyl, or phenyl optionally substituted with F, Cl, CH_3, CH_3O, or CF_3;

R^4 is straight chain C_1-C_8 alkyl optionally substituted with F; C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_7-C_{14} araalkyl where the aryl group is optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl or alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8, or $NCOR^7$; C_3-C_6 alkenyl or alkynyl, C_1-C_3 perfluoroalkyl, phenyl optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8 or $NCOR^7$; pentafluorophenyl, benzyl optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl or alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8, or $NCOR^7$; 2-, 3- or 4-pyridinyl, pyrimidinyl, or biphenyl;

R^5 is H, C_1-C_6 alkyl, or benzyl;

R^6 is H, C_1-C_8 alkyl, C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, C_3-C_8 alkenyl or alkynyl, phenyl optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl or alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8, or $NCOR^7$; pentafluorophenyl, benzyl optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl or alkoxy; F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8, or $NCOR^7$;

R^7 and R^8 are selected independently from H or C_1-C_4 alkyl;

X is $S(O)_r$, O, NR^5, CH_2;

A is C_2-C_{10} alkyl, C_3-C_{10} branched alkyl, C_3-C_{10} alkenyl, or C_3-C_{10} alkynyl;

Y is O, S, H_2;

Z is NHR^4, OR^4, or R^4;

r is 0-2,

and, optionally forming a pharmaceutically acceptable salt thereof.

14. A process of Claim 13 further comprising removing any protecting group on R^3.

15. A process of Claim 13 further comprising reacting a compound of Formula (I) where Y is O with Lawesson's reagent or diphosphorous pentasulfide to yield a compound of Formula (I) where Y is S.

16. A process of Claim 13 further comprising reacting a compound of Formula (I) where Y is O with a reducing agent such as lithium aluminum hydride or sodium borohydride, to yield a compound of Formula (I) where Y is H_2.

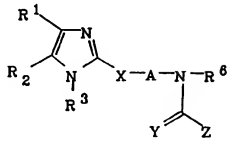
17. A process of Claim 13, further comprising reacting a compound of Formula (I) where X is S with a suitable oxidizing agent to yield either the sulfoxide, SO, where r is 1, or the sulfone, SO_2, where r is 2.

18. A process of Claim 13 further comprising reacting a compound of Formula (I) where R^3 is H with a suitable alkylating agent such as an alkyl halide, to yield a compound of Formula (I) where R^3 is C_1-C_6

alkyl, allyl, or benzyl.

Claims for the following Contracting State : ES

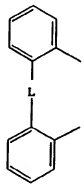
1. A process for preparing a compound of Formula (I):



wherein

R^1 and R^2 are selected independently from H, C_1-C_8 alkyl, provided that when R^1 is H, then R^2 cannot be H and when R^1 is C_1-C_8 alkyl, then R^2 cannot be C_1-C_8 alkyl, C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_7-C_{14} araalkyl, 2-, 3- or 4-pyridinyl, 2-thienyl, 2-furanyl, phenyl optionally substituted with 1 to 3 groups selected from F, Cl, Br, OH, C_1-C_4 alkoxy, C_1-C_4 alkyl, C_3-C_8 branched alkyl, $CH_3S(O)_n$, NO_2, CF_3, or NR^7R^8; or

R^1 and R^2 can also be taken together as



where L is O, $O(CH_2)_{m+1}O$, or $(CH_2)_m$ where m is 0-4;

R^3 is H, C_1-C_6 alkyl, allyl, benzyl, or phenyl optionally substituted with F, Cl, CH_3, CH_3O, or CF_3;

R^4 is straight chain C_1-C_6 alkyl optionally substituted with F; C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_7-C_{14} araalkyl where the aryl group is optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl or alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8, or $NCOR^7$; C_3-C_6 alkenyl or alkynyl, C_1-C_3 perfluoroalkyl, phenyl optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl,C_1-C_4 alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8 or $NCOR^7$; pentafluorophenyl, benzyl optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl or alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8, or $NCOR^7$; 2-, 3- or 4-pyridinyl, pyrimidinyl, or biphenyl;

R^5 is H, C_1-C_6 alkyl, or benzyl;

R^6 is H, C_1-C_6 alkyl, C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, C_3-C_8 alkenyl or alkynyl, phenyl optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl or alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8, or $NCOR^7$; pentafluorophenyl, benzyl optionally substituted with 1 to 3 groups selected from C_1-

C_4 alkyl or alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8, or $NCOR^7$;

R^7 and R^8 are selected independently from H or C_1-C_4 alkyl;

X is $S(O)_n$, O, NR^5, CH_2;

A is C_2-C_{10} alkyl, C_3-C_{10} branched alkyl, C_3-C_{10} alkenyl, or C_3-C_{10} alkynyl;

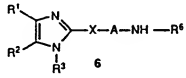
Y is O, S, H_2;

Z is NHR^4, OR^4, or R^4;

r is 0-2,

or a pharmaceutically acceptable salt thereof, comprising the steps of:

reacting a compound of the formula



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where R^1, R^2, X, A, and R^5, are as defined above, and R^3 is as defined above, or a suitable protecting group, such as a silyl or a trityl group,

with:

i) an isocyanate of the formula, R^4-N=C=O, where R^4 is as defined above, to yield a compound of Formula (I) above, where Y is O, and Z is NHR^4; or

ii) an isothiocyanate of the formula, R^4-N=C=S, where R^4 is as defined above, to yield a compound of Formula (I) above, where Y is S, and Z is NHR^4; or

iii) a chloroformate of the formula,

where R^4 is as defined above, to yield a compound of Formula (I) above where Y is O and Z is OR^4; or

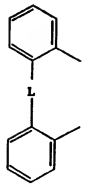
iv) an acid chloride of the formula,

or other activated carboxylic acid, where R^4 is as defined above, to yield a compound of Formula (I) above where Y is O and Z is R^4.

2. A process of Claim 1 wherein

R^1 and R^2 are selected independently from C_1-C_8 alkyl, provided that when R^1 is C_1-C_8 alkyl, then R^2 cannot be C_1-C_8 alkyl, C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_7-C_{14} araalkyl, 2-, 3-, or 4-pyridinyl, 2-thienyl, 2-furanyl, phenyl optionally substituted with 1 to 2 groups selected from F, Cl, Br, OH, C_1-C_4 alkoxy, C_1-C_4 alkyl, C_3-C_8 branched alkyl, $CH_3S(O)_n$, NO_2, CF_3, or NR^7R^8; or

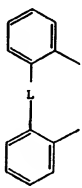
R^1 and R^2 can also be taken together as



where L is O, $O(CH_2)_{m+1}O$, or $(CH_2)_m$ where m is 0-4.

3. A process of Claim 2 wherein
   - R^3 is H, CH_3, phenyl;
   - R^6 is H, C_1-C_8 alkyl, C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, phenyl optionally substituted with 1 to 3 groups selected from CH_3, CH_3O, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, or di(C_1-C_4)-alkylamino; or benzyl optionally substituted with 1 to 3 groups selected from CH_3, CH_3O, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, or di(C_1-C_4)alkylamino;
   - X is S(O)r, CH_2;
   - A is C_2-C_{10} alkyl, C_4-C_9 branched alkyl.

4. A process of Claim 3, wherein R^1 and R^2 are selected independently from C_1-C_8 alkyl, C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_7-C_{14} araalkyl, 2-, 3-, or 4-pyridinyl, 2-thienyl, or phenyl optionally substituted with 1 to 2 groups selected from F, Br, Cl, C_1-C_4 alkyl, C_3-C_8 branched alkyl, CH_3O, $CH_3S(O)_r$, NO_2, CF_3, or di(C_1-C_4)alkylamino; or
   - R^1 and R^2 can also be taken together as



   where L is O or OCH_2O;
   - R^3 is H;
   - R^4 is C_1-C_8 alkyl, C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_7-C_{14} araalkyl, phenyl substituted with 1 to 3 groups selected from CH_3, F, Cl, CH_3O, CN; or benzyl optionally substituted with 1 to 3 groups selected from CH_3, CH_3O, F, Cl, or CN;
   - R^6 is C_1-C_8 alkyl or phenyl optionally substituted with 1 to 3 groups selected from CH_3, CH_3O, F, Cl, or CN;
   - A is C_4-C_9 alkyl;
   - X is $S(O)_r$;
   - Y is O, H_2.

5. A process of claims 1 to 4, wherein the compounds prepared are selected from N'-(2,4-difluorophenyl)-N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptylurea;
N'-(2,4-difluorophenyl)-N-[8-(4,5-diphenyl-1H-imidazol-2-ylthio)octyl]-N-heptylurea;
N-butyl-N'-(2,4 difluorophenyl)-N-[8-(4,5-diphenyl-1H-imidazo]-2-ylthio)octyl]urea;
N'-(2,4-dimethoxyphenyl)-N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptylurea;
N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptyl]-N'-methylurea;
N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptyl-N'-propylurea;
N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N'-(3-fluorophenyl)-N-heptylurea;
N'-(2,4-difluorophenyl)-N-[5-[(4,5-diphenyl-1H-imidazol-2-yl)sulfonyl])pentyl]-N-heptylurea;
N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptyl-N'-(1-methylethyl)urea;
N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-2,4-difluoro-N-heptylbenzeneacetamide;
N'-cyclohexyl-N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)penty]]-N-heptylurea;
N'-(2,4-difluorophenyl)-N-[5-[(4,5-diphenyl-1H-imidazol-2-yl)sulfinyl]pentyl]-N-heptylurea;
N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptylbutanamide;
N-[5-[4,5-bis(1-methylethyl)-1H-imidazol-2-ylthio]pentyl]-N'-(2,4-difluorophenyl)-N-heptylurea;
N-[5-[4,5-bis(1-methylethyl)-1H-imidazol-2-ylthio]pentyl]-N-heptylcyclohexaneacetamide;
N-[5-[4,5-bis(2-methoxyphenyl)-1H-imidazol-2-ylthio]pentyl]-N'-(2,4-difluorophenyl)-N-heptylurea;
phenyl [5-(4,5-diphenyl-1H-imidazol-2-ylthio)penty]]heptylcarbamate;
N-[5-[4,5-bis[4-(dimethylamino)phenyl]-1H-imidazol-2-ylthio]pentyl]-N'-(2,4-difluorophenyl)-N-heptylurea;
N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N'-octyl-N-phenylurea;
N-[5-[4,5-bis(4-methoxyphenyl)-1H-imidazol-2-ylthio]pentyl]-2,4-difluoro-N-heptylbenzeneacetamide;
phenyl [5-[4,5-bis(4-(dimethylamino)phenyl)-1H-imidazol-2-ylthio]pentyl]heptyl]carbamate;
and N-[5-(4,5-dicyclohexyl-1H-imidazol-2-ylthio)pentyl]-N'-(2,4-difluorophenyl)-N-heptylurea.

6. A process of Claim 1 , further comprising removing any protecting group on R^3, to yield a compound of Formula (I), where R^3 is H.

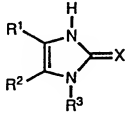
7. A process of Claim 1 , further comprising reacting a compound of Formula (I) where Y is O with Lawesson's reagent or diphosphorous pentasulfide to yield a compound of Formula (I) where Y is S.

8. A process of Claim 1 , further comprising reacting a compound of Formula (I) where Y is O with a reducing agent such as lithium aluminum hydride or sodium borohydride, to yield a compound of Formula (I) where Y is H_2.

9. A process of Claim 1 , further comprising reacting a compound of Formula (I) where X is S with a suitable oxidizing agent to yield either the sulfoxide, SO, where r is 1, or the sulfone, SO_2, where r is 2.

10. A process of Claim 1, further comprising reacting a compound of Formula (I) where R^3 is H with a suitable alkylating agent such as an alkyl halide, to yield a compound of Formula (I) where R^3 is C_1-C_6 alkyl, allyl, or benzyl.

11. A process comprising the steps of alkylating a compound of the formula,

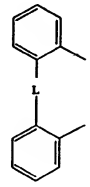


wherein

R^1 and R^2 are selected independently from H, C_1-C_8 alkyl, provided that when R^1 is H, then R^2 cannot be H and when R^1 is C_1-C_8 alkyl, then R^2 cannot be C_1-C_8 alkyl, C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_7-C_{14} araalkyl, 2-, 3- or 4-

pyridinyl, 2-thienyl, 2-furanyl, phenyl optionally substituted with 1 to 3 groups selected from F, Cl, Br, OH, C_1-C_4 alkoxy, C_1-C_4 alkyl, C_3-C_6 branched alkyl, $CH_3S(O)_n$, NO_2, CF_3, or NR^7R^8; or

R^1 and R^2 can also be taken together as

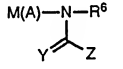


where L is O, $O(CH_2)_{m+1}O$, or $(CH_2)_m$ where m is 0-4;

R^3 is H, C_1-C_6 alkyl, allyl, benzyl, or phenyl optionally substituted with F, Cl, CH_3, CH_3O, CF_3, or an appropriate protecting group, such as a silyl or trityl group, and

X is O or S,

with a compound of the formula,



where

M is halide or tosylate,

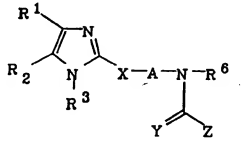
A is C_2-C_{10} alkyl, C_3-C_{10} branched alkyl, C_3-C_{10} alkenyl, or C_3-C_{10} alkynyl;

R^6 is H, C_1-C_8 alkyl, C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, C_3-C_8 alkenyl or alkynyl, phenyl optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl or alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8, or $NCOR^7$; pentafluorophenyl, benzyl optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl or alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8, or $NCOR^7$;

Y is O, S, or H_2, and

Z is NHR^4, OR^4, or R^4,

to yield a compound of Formula (I):

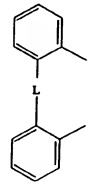


wherein

R^1 and R^2 are selected independently from H, C_1-C_8 alkyl, C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_7-C_{14} araalkyl, 2-, 3- or 4-pyridinyl, 2-thienyl, 2-furanyl,

phenyl optionally substituted with 1 to 3 groups selected from F, Cl, Br, OH, C_1-C_4 alkoxy, C_1-C_4 alkyl, C_3-C_8 branched alkyl, $CH_3S(O)_r$, NO_2, CF_3, or NR^7R^8; or

R^1 and R^2 can also be taken together as



where L is O, $O(CH_2)_{m+1}O$, or $(CH_2)_m$ where m is 0-4;

R^3 is H, C_1-C_6 alkyl, allyl, benzyl, or phenyl optionally substituted with F, Cl, CH_3, CH_3O, or CF_3;

R^4 is straight chain C_1-C_6 alkyl optionally substituted with F; C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_7-C_{14} araalkyl where the aryl group is optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl or alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8, or $NCOR^7$; C_3-C_6 alkenyl or alkynyl, C_1-C_3 perfluoroalkyl, phenyl optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl,C_1-C_4 alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8 or $NCOR^7$; pentafluorophenyl, benzyl optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl or alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8, or $NCOR^7$; 2-, 3- or 4-pyridinyl, pyrimidinyl, or biphenyl;

R^5 is H, C_1-C_6 alkyl, or benzyl;

R^6 is H, C_1-C_8 alkyl, C_3-C_8 branched alkyl, C_3-C_7 cycloalkyl, C_3-C_8 alkenyl or alkynyl, phenyl optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl or alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8, or $NCOR^7$; pentafluorophenyl, benzyl optionally substituted with 1 to 3 groups selected from C_1-C_4 alkyl or alkoxy; F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4 carboalkoxy, NR^7R^8, or $NCOR^7$;

R^7 and R^8 are selected independently from H or C_1-C_4 alkyl;

X is $S(O)_r$, O, NR^5, CH_2;

A is C_2-C_{10} alkyl, C_3-C_{10} branched alkyl, C_3-C_{10} alkenyl, or C_3-C_{10} alkynyl;

Y is O, S, H_2;

Z is NHR^4, OR^4, or R^4;

r is 0-2,

and, optionally forming a pharmaceutically acceptable salt thereof.

12. A process of Claim 11 further comprising removing any protecting group on R^3.

13. A process of Claim 11 further comprising reacting a compound of Formula (I) where Y is O with Lawesson's reagent or diphosphorous pentasulfide to yield a compound of Formula (I) where Y is S.

14. A process of Claim 11 further comprising reacting a compound of Formula (I) where Y is O with a reducing agent such as lithium aluminum hydride or sodium borohydride, to yield a compound of Formula (I) where Y is H_2.

15. A process of Claim 11 further comprising reacting a compound of Formula (I) where X is S with a suitable oxidizing agent to yield either the sulfoxide, SO, where r is 1, or the sulfone, SO_2, where r is 2.

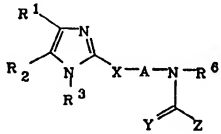
16. A process of Claim 11 further comprising reacting a compound of Formula (I) where R^3 is H with a suitable alkylating agent such as an alkyl halide, to yield a compound of Formula (I) where R^3 is C_1-C_6 alkyl, allyl, or benzyl.

17. A process for preparing a pharmaceutical composition comprising mixing a therapeutically effective amount of a compound prepared according to any one of claims 1 to 16 and a pharmaceutically acceptable carrier.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, GR, IT, LI, LU, NL, SE

1. Verbindung der Formel

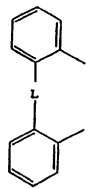


Formel (I)

in welcher

R^1 und R^2 unabhängig ausgewählt sind aus H, C_1-C_8-Alkyl, vorausgesetzt, daß wenn R^1 H ist, R^2 nicht H sein kann und wenn R^1 C_1-C_8-Alkyl ist, R^2 nicht C_1-C_8-Alkyl sein kann, verzweigtem C_3-C_8-Alkyl, C_3-C_7-Cycloalkyl, C_4-C_{10}-Cycloalkylalkyl, C_7-C_{14}-Aralkyl, 2-, 3- oder 4-Pyridinyl, 2-Thienyl, 2-Furanyl, Phenyl, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus F, Cl, Br, OH, C_1-C_6-Alkoxy, C_1-C_6-Alkyl, verzweigtem C_3-C_8-Alkyl, $CH_3S(O)_n$, NO_2, CF_3 oder NR^7R^8 ausgewählt sind, oder

R^1 und R^2 zusammengenommen auch



sein können, worin L O, $O(CH_2)_{m+1}O$ oder $(CH_2)_m$ ist, worin m 0-4 ist,

R^3 H, C_1-C_6-Alkyl, Allyl, Benzyl oder gegebenenfalls mit F, Cl, CH_3, CH_3O oder CF_3 substituiertes Phenyl ist,

R^4 geradkettiges C_1-C_8-Alkyl, das gegebenenfalls mit F substituiert ist, verzweigtes C_3-C_8-Alkyl, C_3-C_7-Cycloalkyl, C_4-C_{10}-Cycloalkylalkyl, C_7-C_{14}-Aralkyl, worin die Arylgruppe gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus C_1-C_4-Alkyl oder -Alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4-Carbalkoxy, NR^7R^8 oder $NCOR^7$ ausgewählt sind, C_3-C_6-Alkenyl oder -Alkinyl, C_1-C_3-Perfluoralkyl, Phenyl, das

gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus C_1-C_4-Alkyl, C_1-C_4-Alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4-Carbalkoxy, NR^7R^8 oder $NCOR^7$ ausgewählt sind, Pentafluorphenyl, Benzyl, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus C_1-C_4-Alkyl oder -Alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4-Carbalkoxy, NR^7R^8 oder $NCOR^7$ ausgewählt sind, 2-, 3- oder 4-Pyridinyl, Pyrimidinyl oder Biphenyl ist,

R^5 H, C_1-C_6-Alkyl oder Benzyl ist,

R^6 H, C_1-C_8-Alkyl, verzweigtes C_3-C_8-Alkyl, C_3-C_7-Cycloalkyl, C_3-C_8-Alkenyl oder -Alkinyl, Phenyl, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus C_1-C_4-Alkyl oder -Alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4-Carbalkoxy, NR^7R^8 oder $NCOR^7$ ausgewählt sind, Pentafluorphenyl, Benzyl ist, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus C_1-C_4-Alkyl oder -Alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4-Carbalkoxy, NR^7R^8 oder $NCOR^7$ ausgewählt sind,

R^7 und R^8 unabhängig aus H oder C_1-C_4-Alkyl ausgewählt sind,

X $S(O)_r$, O, NR^5, CH_2 ist,

A C_2-C_{10}-Alkyl, verzweigtes C_3-C_{10}-Alkyl, C_3-C_{10}-Alkenyl oder C_3-C_{10}-Alkinyl ist,

Y O, S, H_2 ist,

Z NHR^4, OR^4 oder R^4 ist,

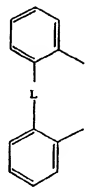
r 0-2 ist,

oder ein pharmazeutisch annehmbares Salz derselben.

2. Verbindung des Anspruchs 1, in welcher

R^1 und R^2 unabhängig ausgewählt sind aus C_1-C_8-Alkyl, vorausgesetzt, daß wenn R^1 C_1-C_8-Alkyl ist, R^2 nicht C_1-C_8-Alkyl sein kann, verzweigtem C_3-C_8-Alkyl, C_3-C_7-Cycloalkyl, C_4-C_{10}-Cycloalkylalkyl, C_7-C_{14}-Aralkyl, 2-, 3- oder 4-Pyridinyl, 2-Thienyl, 2-Furanyl, Phenyl, das gegebenenfalls mit 1 bis 2 Gruppen substituiert ist, die aus F, Cl, Br, OH, C_1-C_4-Alkoxy, C_1-C_4-Alkyl, verzweigtem C_3-C_8-Alkyl, $CH_3S(O)_r$, NO_2, CF_3 oder NR^7R^8 ausgewählt sind, oder

R^1 und R^2 auch als



zusammengenommen werden können, worin L O, $O(CH_2)_{m+1}O$ oder $(CH_2)_m$ ist, worin m 0-4 ist.

3. Verbindung des Anspruchs 2, in welcher

R^3 H, CH_3, Phenyl ist,

R^6 H, C_1-C_8-Alkyl, verzweigtes C_3-C_8-Alkyl, C_3-C_7-Cycloalkyl, Phenyl, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus CH_3, CH_3O, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3 oder Di(C_1-C_4)alkylamino ausgewählt sind, oder Benzyl ist, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus CH_3, CH_3O, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3 oder Di(C_1-C_4)alkylamino ausgewählt sind,

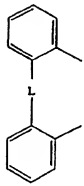
X $S(O)_r$, CH_2 ist,

A C_2-C_{10}-Alkyl, verzweigtes C_4-C_9-Alkyl ist.

4. Verbindung des Anspruchs 3, in welcher

R^1 und R^2 unabhängig ausgewählt sind aus C_1-C_8-Alkyl, verzweigtem C_3-C_8-Alkyl, C_3-C_7-Cycloalkyl, C_4-C_{10}-Cycloalkylalkyl, C_7-C_{14}-Aralkyl, 2-, 3- oder 4-Pyridinyl, 2-Thienyl oder Phenyl, das gegebenenfalls mit 1 bis 2 Gruppen substituiert ist, die aus F, Br, Cl, C_1-C_4-Alkyl, verzweigtem C_3-C_8-Alkyl, CH_3O, $CH_3S(O)_n$, NO_2, CF_3 oder $Di(C_1$-$C_4)$-alkylamino ausgewählt sind, oder

R^1 und R^2 auch als



zusammengenommen werden können, worin L O oder OCH_2O ist,

R^3 H ist,

R^4 C_1-C_8-Alkyl, verzweigtes C_3-C_8-Alkyl, C_3-C_7-Cycloalkyl, C_4-C_{10}-Cycloalkylalkyl, C_7-C_{14}-Aralkyl, Phenyl, das mit 1 bis 3 Gruppen substituiert ist, die aus CH_3, F, Cl, CH_3O, CN ausgewählt sind, oder Benzyl ist, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus CH_3, CH_3O, F, Cl oder CN ausgewählt sind,

R^6 C_1-C_8-Alkyl oder Phenyl ist, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus CH_3, CH_3O, F, Cl oder CN ausgewählt sind,

A C_4-C_9-Alkyl ist,

X $S(O)_r$ ist,

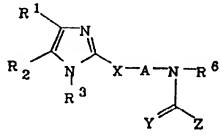
Y O, H_2 ist.

5. Verbindungen der Ansprüche 1 bis 4, die aus
N'-(2,4-Difluorphenyl)-N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptylharnstoff,
N'-(2,4-Difluorphenyl)-N-[8-(4,5-diphenyl-1H-imidazol-2-ylthio)octyl]-N-heptylharnstoff,
N-Butyl-N'-(2,4-difluorphenyl)-N-[8-(4,5-diphenyl-1H-imidazol-2-ylthio)octyl]harnstoff,
N'-(2,4-Dimethoxyphenyl)-N-[5-(4,5-diphenyl-1H-imidazol-2-yl-thio)pentyl]-N-heptylharnstoff,
N-[5-(4,5-Diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptyl-N'-methylharnstoff,
N-[5-(4,5-Diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptyl-N'-propylharnstoff,
N-[5-(4,5-Diphenyl-1H-imidazol-2-ylthio)pentyl]-N'-(3-fluorphenyl)-N-heptylharnstoff,
N'-(2,4-Difluorphenyl)-N-[5-[(4,5-Diphenyl-1H-imidazol-2-yl)sulfonyl]pentyl]-N-heptylharnstoff,
N-[5-(4,5-Diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptyl-N'-(1-methylethyl)harnstoff,
N-[5-(4,5-Diphenyl-1H-imidazol-2-ylthio)pentyl]-2,4-difluor-N-heptylbenzolacetamid,
N'-Cyclohexyl-N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl)-N-heptylharnstoff,
N'-(2,4-Difluorphenyl)-N-[5-[(4,5-Diphenyl-1H-imidazol-2-yl)sulfinyl]pentyl]-N-heptylharnstoff,
N-[5-(4,5-Diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptylbutanamid,
N-[5-[4,5-Bis(1-methylethyl)-1H-imidazol-2-ylthio]pentyl]-N'-(2,4-difluorphenyl)-N-heptylharnstoff,
N-[5-[4,5-Bis(1-methylethyl)-1H-imidazol-2-ylthio]pentyl]-N-heptylcyclohexanacetamid,
N-[5-[4,5-Bis(2-methoxyphenyl)-1H-imidazol-2-ylthio]pentyl]-N'-(2,4-difluorphenyl)-N-heptylharnstoff,
[5-(4,5-Diphenyl-1H-imidazol-2-ylthio)pentyl]heptylcarbaminsäure-phenylester,
N-[5-[4,5-Bis[4-(dimethylamino)phenyl]-1H-imidazol-2-ylthio]pentyl]-N'-(2,4-difluorphenyl)-N-heptylharnstoff,
N-[5-(4,5-Diphenyl-1H-imidazol-2-ylthio)pentyl]-N'-octyl-N-phenylharnstoff,
N-[5-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylthio]pentyl]-2,4-difluor-N-heptylbenzolacetamid,
[5-[4,5-Bis(4-(dimethylamino)phenyl)-1H-imidazol-2-ylthio]pentyl]heptylcarbaminsäure-phenylester und

N-[5-(4,5-Dicyclohexyl-1H-imidazol-2-ylthio)pentyl]-N'-(2,4-difluorphenyl)-N-heptylharnstoff ausgewählt sind.

6. Pharmazeutische Zusammensetzung umfassend eine therapeutisch wirksame Menge einer Verbindung der Ansprüche 1 bis 5 und einen pharmazeutisch annehmbaren Träger.

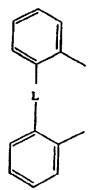
7. Verfahren zum Herstellen einer Verbindung der Formel (I)



in welcher

R^1 und R^2 unabhängig ausgewählt sind aus H, C_1-C_8-Alkyl, vorausgesetzt, daß wenn R^1 H ist, R^2 nicht H sein kann und wenn R^1 C_1-C_8-Alkyl ist, R^2 nicht C_1-C_8-Alkyl sein kann, verzweigtem C_3-C_8-Alkyl, C_3-C_7-Cycloalkyl, C_4-C_{10}-Cycloalkylalkyl, C_7-C_{14}-Aralkyl, 2-, 3- oder 4-Pyridinyl, 2-Thienyl, 2-Furanyl, Phenyl, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus F, Cl, Br, OH, C_1-C_4-Alkoxy, C_1-C_4-Alkyl, verzweigtem C_3-C_8-Alkyl, $CH_3S(O)_t$, NO_2, CF_3 oder NR^7R^8 ausgewählt sind, oder

R^1 und R^2 zusammengenommen auch



sein können, worin L O, $O(CH_2)_{m+1}O$ oder $(CH_2)_m$ ist, worin m 0-4 ist,

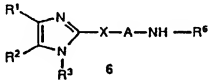
R^3 H, C_1-C_6-Alkyl, Allyl, Benzyl oder gegebenenfalls mit F, Cl, CH_3, CH_3O oder CF_3 substituiertes Phenyl ist,

R^4 geradkettiges C_1-C_6-Alkyl, das gegebenenfalls mit F substituiert ist, verzweigtes C_3-C_8-Alkyl, C_3-C_7-Cycloalkyl, C_4-C_{10}-Cycloalkylalkyl, C_7-C_{14}-Aralkyl, worin die Arylgruppe gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus C_1-C_4-Alkyl oder -Alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4-Carbalkoxy, NR^7R^8 oder $NCOR^7$ ausgewählt sind, C_3-C_6-Alkenyl oder -Alkinyl, C_1-C_3-Perfluoralkyl, Phenyl, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus C_1-C_4-Alkyl, C_1-C_4-Alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4-Carbalkoxy, NR^7R^8 oder $NCOR^7$ ausgewählt sind, Pentafluorphenyl, Benzyl, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus C_1-C_4-Alkyl oder -Alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4-Carbalkoxy, NR^7R^8 oder $NCOR^7$ ausgewählt sind, 2-, 3- oder 4-Pyridinyl, Pyrimidinyl oder Biphenyl ist,

R^5 H, C_1-C_6-Alkyl oder Benzyl ist,

R^6	H, C_1-C_6-Alkyl, verzweigtes C_3-C_6-Alkyl, C_3-C_7-Cycloalkyl, C_3-C_6-Alkenyl oder -Alkinyl, Phenyl, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus C_1-C_4-Alkyl oder -Alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4-Carbalkoxy, NR^7R^8 oder $NCOR^7$ ausgewählt sind, Pentafluorphenyl, Benzyl ist, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus C_1-C_4-Alkyl oder -Alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4-Carbalkoxy, NR^7R^8 oder $NCOR^7$ ausgewählt sind,
R^7 und R^8	unabhängig aus H oder C_1-C_4-Alkyl ausgewählt sind,
X	$S(O)_r$, O, NR^5, CH_2 ist,
A	C_2-C_{10}-Alkyl, verzweigtes C_3-C_{10}-Alkyl, C_3-C_{10}-Alkenyl oder C_3-C_{10}-Alkinyl ist,
Y	O, S, H_2 ist,
Z	NHR^4, OR^4 oder R^4 ist,
r	0-2 ist,

oder eines pharmazeutisch annehmbaren Salzes derselben, umfas send die Schritte des Umsetzens einer Verbindung der Formel



6

worin R^1, R^2, X, A und R^6 wie vorstehend definiert sind, und R^3 wie vorstehend definiert oder eine geeignete Schutzgruppe ist, wie etwa eine Silyl- oder Tritylgruppe, mit

i) einem Isocyanat der Formel R^4-N = C = O, worin R^4 wie vorstehend definiert ist, unter Liefern einer Verbindung der vorstehenden Formel (I), worin Y O ist und Z NHR^4 ist, oder

ii) einem Isothiocyanat der Formel R^4-N = C = S, worin R^4 wie vorstehend definiert ist, unter Liefern einer Verbindung der vorstehenden Formel (I), worin Y S ist und Z NHR^4 ist, oder

iii) einem Chlorameisensäureester der Formel

worin R^4 wie vorstehend definiert ist, unter Ergeben einer Verbindung der vorstehenden Formel (I), worin Y O ist und Z OR^4 ist, oder

iv) einem Säurechlorid der Formel

oder einer anderen aktivierten Carbonsäure, worin R^4 wie vorstehend definiert ist, unter Liefern einer Verbindung der vorstehenden Formel (I), worin Y O ist und Z R^4 ist.

8. Verfahren des Anspruchs 7, das weiter das Entfernen einer etwaigen Schutzgruppe an R^3 unter Liefern einer Verbindung der Formel (I), worin R^3 H ist, umfaßt.

9. Verfahren des Anspruchs 7, das weiter das Umsetzen einer Verbindung der Formel (I), worin Y O ist, mit Lawessons Reagenz oder Diphosphorpentasulfid unter Liefern einer Verbindung der Formel (I),

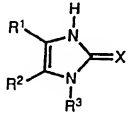
worin Y S ist, umfaßt.

10. Verfahren des Anspruchs 7, das weiter das Umsetzen einer Verbindung der Formel (I), worin Y O ist, mit einem Reduktionsmittel, wie etwa Lithiumaluminiumhydrid oder Natriumborhydrid, unter Liefern einer Verbindung der Formel (I), worin Y H_2 ist, umfaßt.

11. Verfahren des Anspruchs 7, das weiter das Umsetzen einer Verbindung der Formel (I), worin X S ist, mit einem geeigneten Oxidationsmittel unter Liefern entweder des Sulfoxids SO, wobei r 1 ist, oder des Sulfons SO_2, wobei r 2 ist, umfaßt.

12. Verfahren des Anspruchs 7, das weiter das Umsetzen einer Verbindung der Formel (I), worin R^3 H ist, mit einem geeigneten Alkylierungsmittel wie etwa einem Alkylhalogenid unter Liefern einer Verbindung der Formel (I), worin R^3 C_1-C_6-Alkyl, Allyl oder Benzyl ist, umfaßt.

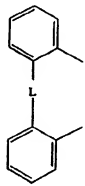
13. Verfahren, umfassend die Schritte des Alkylierens einer Verbindung der Formel



in welcher

R^1 und R^2 unabhängig ausgewählt sind aus H, C_1-C_8-Alkyl, vorausgesetzt, daß wenn R^1 H ist, R^2 nicht H sein kann und wenn R^1 C_1-C_8-Alkyl ist, R^2 nicht C_1-C_8-Alkyl sein kann, verzweigtem C_3-C_8-Alkyl, C_3-C_7-Cycloalkyl, C_4-C_{10}-Cycloalkylalkyl, C_7-C_{14}-Aralkyl, 2-, 3- oder 4-Pyridinyl, 2-Thienyl, 2-Furanyl, Phenyl, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus F, Cl, Br, OH, C_1-C_4-Alkoxy, C_1-C_4-Alkyl, verzweigtem C_3-C_8-Alkyl, $CH_3S(O)_n$, NO_2, CF_3 oder NR^7R^8 ausgewählt sind, oder

R^1 und R^2 zusammengenommen auch

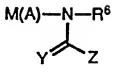


sein können, worin L O, $O(CH_2)_{m+1}O$ oder $(CH_2)_m$ ist, worin m 0-4 ist,

R^3 H, C_1-C_6-Alkyl, Allyl, Benzyl oder gegebenenfalls mit F, Cl, CH_3, CH_3O oder CF_3 substituiertes Phenyl, oder eine geeignete Schutzgruppe ist, wie etwa eine Silyl- oder Tritylgruppe, und

X O oder S ist,

mit einer Verbindung der Formel



worin

M ein Halogenid oder Tosylat ist,

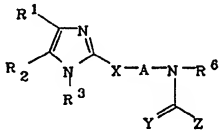
A C_2-C_{10}-Alkyl, verzweigtes C_3-C_{10}-Alkyl, C_3-C_{10}-Alkenyl oder C_3-C_{10}-Alkinyl ist,

R^6 H, C_1-C_8-Alkyl, verzweigtes C_3-C_8-Alkyl, C_3-C_7-Cycloalkyl, C_3-C_8-Alkenyl oder -Alkinyl, Phenyl, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus C_1-C_4-Alkyl oder -Alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4-Carbalkoxy, NR^7R^8 oder $NCOR^7$ ausgewählt sind, Pentafluorphenyl, Benzyl ist, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus C_1-C_4-Alkyl oder -Alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4-Carbalkoxy, NR^7R^8 oder $NCOR^7$ ausgewählt sind,

Y O, S oder H_2 ist und

Z NHR^4, OR^4 oder R^4 ist,

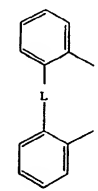
unter Liefern einer Verbindung der Formel (I)



in welcher

R^1 und R^2 unabhängig ausgewählt sind aus H, C_1-C_8-Alkyl, verzweigtem C_3-C_8-Alkyl, C_3-C_7-Cycloalkyl, C_4-C_{10}-Cycloalkylalkyl, C_7-C_{14}-Aralkyl, 2-, 3- oder 4-Pyridinyl, 2-Thienyl, 2-Furanyl, Phenyl, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus F, Cl, Br, OH, C_1-C_4-Alkoxy, C_1-C_4-Alkyl, verzweigtem C_3-C_8-Alkyl, $CH_3S(O)_n$, NO_2, CF_3 oder NR^7R^8 ausgewählt sind, oder

R^1 und R^2 zusammengenommen auch



sein können, worin L O, $O(CH_2)_{m+1}O$ oder $(CH_2)_m$ ist, worin m 0-4 ist,

R^3 H, C_1-C_6-Alkyl, Allyl, Benzyl oder gegebenenfalls mit F, Cl, CH_3, CH_3O oder CF_3 substituiertes Phenyl ist,

R^4 geradkettiges C_1-C_8-Alkyl, das gegebenenfalls mit F substituiert ist, verzweigtes C_3-

C_8-Alkyl, C_3-C_7-Cycloalkyl, C_4-C_{10}-Cycloalkylalkyl, C_7-C_{14}-Aralkyl, worin die Arylgruppe gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus C_1-C_4-Alkyl oder -Alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4-Carbalkoxy, NR^7R^8 oder $NCOR^7$ ausgewählt sind, C_3-C_6-Alkenyl oder -Alkinyl, C_1-C_3-Perfluoralkyl, Phenyl, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus C_1-C_4-Alkyl, C_1-C_4-Alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4-Carbalkoxy, NR^7R^8 oder $NCOR^7$ ausgewählt sind, Pentafluorphenyl, Benzyl, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus C_1-C_4-Alkyl oder -Alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4-Carbalkoxy, NR^7R^8 oder $NCOR^7$ ausgewählt sind, 2-, 3- oder 4-Pyridinyl, Pyrimidinyl oder Biphenyl ist,

R^5 H, C_1-C_6-Alkyl oder Benzyl ist,

R^6 H, C_1-C_8-Alkyl, verzweigtes C_3-C_8-Alkyl, C_3-C_7-Cycloalkyl, C_3-C_8-Alkenyl oder -Alkinyl, Phenyl, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus C_1-C_4-Alkyl oder -Alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4-Carbalkoxy, NR^7R^8 oder $NCOR^7$ ausgewählt sind, Pentafluorphenyl, Benzyl ist, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus C_1-C_4-Alkyl oder -Alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4-Carbalkoxy, NR^7R^8 oder $NCOR^7$ ausgewählt sind,

R^7 und R^8 unabhängig aus H oder C_1-C_4-Alkyl ausgewählt sind,

X $S(O)_n$, O, NR^5, CH_2 ist,

A C_2-C_{10}-Alkyl, verzweigtes C_3-C_{10}-Alkyl, C_3-C_{10}-Alkenyl oder C_3-C_{10}-Alkinyl ist,

Y O, S, H_2 ist,

Z NHR^4, OR^4 oder R^4 ist,

r 0-2 ist,

und gegebenenfalls das Bilden eines pharmazeutisch annehmbaren Salzes derselben.

14. Verfahren des Anspruchs 13, das weiter das Entfernen einer etwaigen Schutzgruppe an R^3 umfaßt.

15. Verfahren des Anspruchs 13, das weiter das Umsetzen einer Verbindung der Formel (I), worin Y O ist, mit Lawessons Reagenz oder Diphosphorpentasulfid unter Liefern einer Verbindung der Formel (I), worin Y S ist, umfaßt.

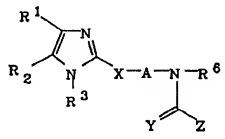
16. Verfahren des Anspruchs 13, das weiter das Umsetzen einer Verbindung der Formel (I), worin Y O ist, mit einem Reduktionsmittel, wie etwa Lithiumaluminiumhydrid oder Natriumborhydrid, unter Liefern einer Verbindung der Formel (I), worin Y H_2 ist, umfaßt.

17. Verfahren des Anspruchs 13, das weiter das Umsetzen einer Verbindung der Formel (I), worin X S ist, mit einem geeigneten Oxidationsmittel unter Liefern entweder des Sulfoxids SO, wobei r 1 ist, oder des Sulfons SO_2, wobei r 2 ist, umfaßt.

18. Verfahren des Anspruchs 13, das weiter das Umsetzen einer Verbindung der Formel (I), worin R^3 H ist, mit einem geeigneten Alkylierungsmittel wie etwa einem Alkylhalogenid unter Liefern einer Verbindung der Formel (I), worin R^3 C_1-C_6-Alkyl, Allyl oder Benzyl ist, umfaßt.

Patentansprüche für den Vertragsstaat : ES

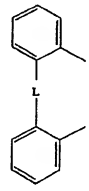
1. Verfahren zur Herstellung einer Verbindung der Formel (I)



in welcher

R^1 und R^2 unabhängig ausgewählt sind aus H, C_1-C_8-Alkyl, vorausgesetzt, daß wenn R^1 H ist, R^2 nicht H sein kann und wenn R^1 C_1-C_8-Alkyl ist, R^2 nicht C_1-C_8-Alkyl sein kann, verzweigtem C_3-C_8-Alkyl, C_3-C_7-Cycloalkyl, C_4-C_{10}-Cycloalkylalkyl, C_7-C_{14}-Aralkyl, 2-, 3- oder 4-Pyridinyl, 2-Thienyl, 2-Furanyl, Phenyl, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus F, Cl, Br, OH, C_1-C_4-Alkoxy, C_1-C_4-Alkyl, verzweigtem C_3-C_8-Alkyl, $CH_3S(O)_n$, NO_2, CF_3 oder NR^7R^8 ausgewählt sind, oder

R^1 und R^2 zusammengenommen auch



sein können, worin L O, $O(CH_2)_{m+1}O$ oder $(CH_2)_m$ ist, worin m 0-4 ist,

R^3 H, C_1-C_6-Alkyl, Allyl, Benzyl oder gegebenenfalls mit F, Cl, CH_3, CH_3O oder CF_3 substituiertes Phenyl ist,

R^4 geradkettiges C_1-C_8-Alkyl, das gegebenenfalls mit F substituiert ist, verzweigtes C_3-C_8-Alkyl, C_3-C_7-Cycloalkyl, C_4-C_{10}-Cycloalkylalkyl, C_7-C_{14}-Aralkyl, worin die Arylgruppe gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus C_1-C_4-Alkyl oder -Alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4-Carbalkoxy, NR^7R^8 oder $NCOR^7$ ausgewählt sind, C_3-C_6-Alkenyl oder -Alkinyl, C_1-C_3-Perfluoralkyl, Phenyl, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus C_1-C_4-Alkyl, C_1-C_4-Alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4-Carbalkoxy, NR^7R^8 oder $NCOR^7$ ausgewählt sind, Pentafluorphenyl, Benzyl, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus C_1-C_4-Alkyl oder -Alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4-Carbalkoxy, NR^7R^8 oder $NCOR^7$ ausgewählt sind, 2-, 3- oder 4-Pyridinyl, Pyrimidinyl oder Biphenyl ist,

R^5 H, C_1-C_6-Alkyl oder Benzyl ist,

R^6 H, C_1-C_8-Alkyl, verzweigtes C_3-C_8-Alkyl, C_3-C_7-Cycloalkyl, C_3-C_8-Alkenyl oder -Alkinyl, Phenyl, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus C_1-C_4-Alkyl oder -Alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4-Carbalkoxy, NR^7R^8 oder $NCOR^7$ ausgewählt sind, Pentafluorphenyl, Benzyl, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus C_1-C_4-Alkyl oder -Alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4-Carbalkoxy, NR^7R^8 oder $NCOR^7$ ausgewählt sind,

R^7 und R^8 unabhängig aus H oder C_1-C_4-Alkyl ausgewählt sind,

X $S(O)_r$, O, NR^5, CH_2 ist,

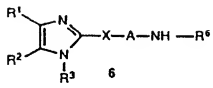
A C_2-C_{10}-Alkyl, verzweigtes C_3-C_{10}-Alkyl, C_3-C_{10}-Alkenyl oder C_3-C_{10}-Alkinyl ist,

Y O, S, H_2 ist,

Z NHR^4, OR^4 oder R^4 ist,

r 0-2 ist,

oder eines pharmazeutisch annehmbaren Salzes derselben, umfassend die Schritte des Umsetzens einer Verbindung der Formel



6

worin R^1, R^2, X, A und R^5 wie vorstehend definiert sind, und R^3 wie vorstehend definiert oder eine geeignete Schutzgruppe ist, wie etwa eine Silyl- oder Tritylgruppe, mit

i) einem Isocyanat der Formel R^4-N=C=O, worin R^4 wie vorstehend definiert ist, unter Liefern einer Verbindung der vorstehenden Formel (I), worin Y O ist und Z NHR^4 ist, oder

ii) einem Isothiocyanat der Formel R^4-N=C=S, worin R^4 wie vorstehend definiert ist, unter Liefern einer Verbindung der vorstehenden Formel (I), worin Y S ist und Z NHR^4 ist, oder

iii) einem Chlorameisensäureester der Formel

worin R^4 wie vorstehend definiert ist, unter Ergeben einer Verbindung der vorstehenden Formel (I), worin Y O ist und Z OR^4 ist, oder

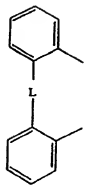
iv) einem Säurechlorid der Formel

oder einer anderen aktivierten Carbonsäure, worin R^4 wie vorstehend definiert ist, unter Liefern einer Verbindung der vorstehenden Formel (I), worin Y O ist und Z R^4 ist.

2. Verfahren des Anspruchs 1, bei welchem

R^1 und R^2 unabhängig ausgewählt sind aus C_1-C_8-Alkyl, vorausgesetzt, daß wenn R^1 C_1-C_8-Alkyl ist, R^2 nicht C_1-C_8-Alkyl sein kann, verzweigtem C_3-C_8-Alkyl, C_3-C_7-Cycloalkyl, C_4-C_{10}-Cycloalkylalkyl, C_7-C_{14}-Aralkyl, 2-, 3- oder 4-Pyridinyl, 2-Thienyl, 2-Furanyl, Phenyl, das gegebenenfalls mit 1 bis 2 Gruppen substituiert ist, die aus F, Cl, Br, OH, C_1-C_4-Alkoxy, C_1-C_4-Alkyl, verzweigtem C_3-C_8-Alkyl, $CH_3S(O)_n$, NO_2, CF_3 oder NR^7R^8 ausgewählt sind, oder

R^1 und R^2 auch als



zusammengenommen werden können, worin L O, $O(CH_2)_{m+1}O$ oder $(CH_2)_m$ ist, worin m 0-4 ist.

3. Verfahren des Anspruchs 2, bei welchem

R^3 H, CH_3, Phenyl ist,

R^6 H, C_1-C_8-Alkyl, verzweigtes C_3-C_8-Alkyl, C_3-C_7-Cycloalkyl, Phenyl, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus CH_3, CH_3O, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3 oder Di(C_1-C_4)alkylamino ausgewählt sind, oder Benzyl ist, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus CH_3, CH_3O, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3 oder Di(C_1-C_4)alkylamino ausgewählt sind,

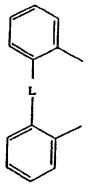
X $S(O)_n$, CH_2 ist,

A C_2-C_{10}-Alkyl, verzweigtes C_4-C_9-Alkyl ist.

4. Verfahren des Anspruchs 3, bei welchem

R^1 und R^2 unabhängig ausgewählt sind aus C_1-C_8-Alkyl, verzweigtem C_3-C_8-Alkyl, C_3-C_7-Cycloalkyl, C_4-C_{10}-Cycloalkylalkyl, C_7-C_{14}-Aralkyl, 2-, 3- oder 4-Pyridinyl, 2-Thienyl oder Phenyl, das gegebenenfalls mit 1 bis 2 Gruppen substituiert ist, die aus F, Br, Cl, C_1-C_4-Alkyl, verzweigtem C_3-C_8-Alkyl, CH_3O, $CH_3S(O)_n$, NO_2, CF_3 oder Di(C_1-C_4)-alkylamino ausgewählt sind, oder

R^1 und R^2 auch als



zusammengenommen werden können, worin L O oder OCH_2O ist,

R^3 H ist,

R^4 C_1-C_8-Alkyl, verzweigtes C_3-C_8-Alkyl, C_3-C_7-Cycloalkyl, C_4-C_{10}-Cycloalkylalkyl, C_7-C_{14}-Aralkyl, Phenyl, das mit 1 bis 3 Gruppen substituiert ist, die aus CH_3, F, Cl, CH_3O, CN ausgewählt sind, oder Benzyl ist, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus CH_3, CH_3O, F, Cl oder CN ausgewählt sind,

R^6 C_1-C_8-Alkyl oder Phenyl ist, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus CH_3, CH_3O, F, Cl oder CN ausgewählt sind,

A C_4-C_9-Alkyl ist,

X S(O)$_r$ ist,
Y O, H_2 ist.

5. Verfahren der Ansprüche 1 bis 4, wobei die hergestellten Verbindungen aus
N'-(2,4-Difluorphenyl)-N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptylharnstoff,
N'-(2,4-Difluorphenyl)-N-[8-(4,5-diphenyl-1H-imidazol-2-ylthio)octyl]-N-heptylharnstoff,
N-Butyl-N'-(2,4-difluorphenyl)-N-[8-(4,5-diphenyl-1H-imidazol-2-ylthio)octyl]harnstoff,
N'-(2,4-Dimethoxyphenyl)-N-[5-(4,5-diphenyl-1H-imidazol-2-yl-thio)pentyl]-N-heptylharnstoff,
N-[5-(4,5-Diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptyl-N'-methylharnstoff,
N-[5-(4,5-Diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptyl-N'-propylharnstoff,
N-[5-(4,5-Diphenyl-1H-imidazol-2-ylthio)pentyl]-N'-(3-fluorphenyl)-N-heptylharnstoff,
N'-(2,4-Difluorphenyl)-N-[5-[(4,5-Diphenyl-1H-imidazol-2-yl)sulfonyl]pentyl]-N-heptylharnstoff,
N-[5-(4,5-Diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptyl-N'-(1-methylethyl)harnstoff,
N-[5-(4,5-Diphenyl-1H-imidazol-2-ylthio)pentyl]-2,4-difluor-N-heptylbenzolacetamid,
N'-Cyclohexyl-N-[5-(4,5-diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptylharnstoff,
N'-(2,4-Difluorphenyl)-N-[5-[(4,5-Diphenyl-1H-imidazol-2-yl)sulfinyl]pentyl]-N-heptylharnstoff,
N-[5-(4,5-Diphenyl-1H-imidazol-2-ylthio)pentyl]-N-heptylbutanamid,
N-[5-[4,5-Bis(1-methylethyl)-1H-imidazol-2-ylthio]pentyl]-N'-(2,4-difluorphenyl)-N-heptylharnstoff,
N-[5-[4,5-Bis(1-methylethyl)-1H-imidazol-2-ylthio]pentyl]-N-heptylcyclohexanacetamid,
N-[5-[4,5-Bis(2-methoxyphenyl)-1H-imidazol-2-ylthio]pentyl]-N'-(2,4-difluorphenyl)-N-heptylharnstoff,
[5-(4,5-Diphenyl-1H-imidazol-2-ylthio)pentyl]heptylcarbaminsäure-phenylester,
N-[5-[4,5-Bis[4-(dimethylamino)phenyl]-1H-imidazol-2-ylthio]pentyl]-N'-(2,4-difluorphenyl)-N-heptylharnstoff,
N-[5-(4,5-Diphenyl-1H-imidazol-2-ylthio)pentyl]-N'-octyl-N-phenylharnstoff,
N-[5-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylthio]pentyl]-2,4-difluor-N-heptylbenzolacetamid,
[5-[4,5-Bis(4-(dimethylamino)phenyl)-1H-imidazol-2-ylthio]pentyl]heptylcarbaminsäure-phenylester und
N-[5-(4,5-Dicyclohexyl-1H-imidazol-2-ylthio)pentyl]-N'-(2,4-difluorphenyl)-N-heptylharnstoff ausgewählt sind.

6. Verfahren des Anspruchs 1, das weiter das Entfernen einer etwaigen Schutzgruppe an R^3 unter Liefern einer Verbindung der Formel (I), worin R^3 H ist, umfaßt.

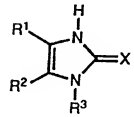
7. Verfahren des Anspruchs 1, das weiter das Umsetzen einer Verbindung der Formel (I), worin Y O ist, mit Lawessons Reagenz oder Diphosphorpentasulfid unter Liefern einer Verbindung der Formel (I), worin Y S ist, umfaßt.

8. Verfahren des Anspruchs 1, das weiter das Umsetzen einer Verbindung der Formel (I), worin Y O ist, mit einem Reduktionsmittel, wie etwa Lithiumaluminiumhydrid oder Natriumborhydrid, unter Liefern einer Verbindung der Formel (I), worin Y H_2 ist, umfaßt.

9. Verfahren des Anspruchs 1, das weiter das Umsetzen einer Verbindung der Formel (I), worin X S ist mit einem geeigneten Oxidationsmittel unter Liefern entweder des Sulfoxids SO, wobei r 1 ist, oder des Sulfons SO_2, wobei r 2 ist, umfaßt.

10. Verfahren des Anspruchs 1, das weiter das Umsetzen einer Verbindung der Formel (I), worin R^3 H ist, mit einem geeigneten Alkylierungsmittel wie etwa einem Alkylhalogenid unter Liefern einer Verbindung der Formel (I), worin R^3 C_1-C_6-Alkyl, Allyl oder Benzyl ist, umfaßt.

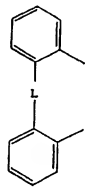
11. Verfahren, umfassend die Schritte des Alkylierens einer Verbindung der Formel



in welcher

R^1 und R^2 unabhängig ausgewählt sind aus H, C_1-C_8-Alkyl, vorausgesetzt, daß wenn R^1 H ist, R^2 nicht H sein kann und wenn R^1 C_1-C_8-Alkyl ist, R^2 nicht C_1-C_8-Alkyl sein kann, verzweigtem C_3-C_8-Alkyl, C_3-C_7-Cycloalkyl, C_4-C_{10}-Cycloalkylalkyl, C_7-C_{14}-Aralkyl, 2-, 3- oder 4-Pyridinyl, 2-Thienyl, 2-Furanyl, Phenyl, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus F, Cl, Br, OH, C_1-C_4-Alkoxy, C_1-C_4-Alkyl, verzweigtem C_3-C_8-Alkyl, $CH_3S(O)_r$, NO_2, CF_3 oder NR^7R^8 ausgewählt sind, oder

R^1 und R^2 zusammengenommen auch

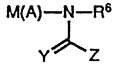


sein können, worin L O, $O(CH_2)_{m+1}O$ oder $(CH_2)_m$ ist, worin m 0-4 ist,

R^3 H, C_1-C_6-Alkyl, Allyl, Benzyl oder gegebenenfalls mit F, Cl, CH_3, CH_3O oder CF_3 substituiertes Phenyl, oder eine geeignete Schutzgruppe ist, wie etwa eine Silyl- oder Tritylgruppe, und

X O oder S ist,

mit einer Verbindung der Formel



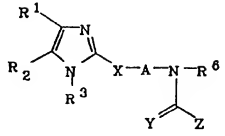
worin

M ein Halogenid oder Tosylat ist,

A C_2-C_{10}-Alkyl, verzweigtes C_3-C_{10}-Alkyl, C_3-C_{10}-Alkenyl oder C_3-C_{10}-Alkinyl ist,

R^6 H, C_1-C_8-Alkyl, verzweigtes C_3-C_8-Alkyl, C_3-C_7-Cycloalkyl, C_3-C_8-Alkenyl oder -Alkinyl, Phenyl, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus C_1-C_4-Alkyl oder -Alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4-Carbalkoxy, NR^7R^8 oder $NCOR^7$ ausgewählt sind, Pentafluorphenyl, Benzyl ist, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus C_1-C_4-Alkyl oder -Alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4-Carbalkoxy, NR^7R^8 oder $NCOR^7$ ausgewählt sind,

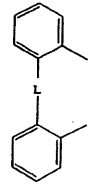
Y O, S oder H_2 ist und
Z NHR^4, OR^4 oder R^4 ist,
unter Liefern einer Verbindung der Formel (I)



in welcher

R^1 und R^2 unabhängig ausgewählt sind aus H, C_1-C_8-Alkyl, verzweigtem C_3-C_8-Alkyl, C_3-C_7-Cycloalkyl, C_4-C_{10}-Cycloalkylalkyl, C_7-C_{14}-Aralkyl, 2-, 3- oder 4-Pyridinyl, 2-Thienyl, 2-Furanyl, Phenyl, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus F, Cl, Br, OH, C_1-C_4-Alkoxy, C_1-C_4-Alkyl, verzweigtem C_3-C_8-Alkyl, $CH_3S(O)_n$, NO_2, CF_3 oder NR^7R^8 ausgewählt sind, oder

R^1 und R^2 zusammengenommen auch



sein können, worin L O, $O(CH_2)_{m+1}O$ oder $(CH_2)_m$ ist, worin m 0-4 ist,

R^3 H, C_1-C_6-Alkyl, Allyl, Benzyl oder gegebenenfalls mit F, Cl, CH_3, CH_3O oder CF_3 substituiertes Phenyl ist,

R^4 geradkettiges C_1-C_8-Alkyl, das gegebenenfalls mit F substituiert ist, verzweigtes C_3-C_8-Alkyl, C_3-C_7-Cycloalkyl, C_4-C_{10}-Cycloalkylalkyl, C_7-C_{14}-Aralkyl, worin die Arylgruppe gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus C_1-C_4-Alkyl oder -Alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4-Carbalkoxy, NR^7R^8 oder $NCOR^7$ ausgewählt sind, C_3-C_6-Alkenyl oder -Alkinyl, C_1-C_3-Perfluoralkyl, Phenyl, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus C_1-C_4-Alkyl, C_1-C_4-Alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4-Carbalkoxy, NR^7R^8 oder $NCOR^7$ ausgewählt sind, Pentafluorphenyl, Benzyl, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus C_1-C_4-Alkyl oder -Alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4-Carbalkoxy, NR^7R^8 oder $NCOR^7$ ausgewählt sind, 2-, 3- oder 4-Pyridinyl, Pyrimidinyl oder Biphenyl ist,

R^5 H, C_1-C_6-Alkyl oder Benzyl ist,

R^6 H, C_1-C_8-Alkyl, verzweigtes C_3-C_8-Alkyl, C_3-C_7-Cycloalkyl, C_3-C_8-Alkenyl oder -Alkinyl, Phenyl, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus C_1-C_4-Alkyl oder -Alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4-Carbalkoxy, NR^7R^8 oder $NCOR^7$ ausgewählt sind, Pentafluorphenyl, Benzyl ist, das gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die aus C_1-C_4-Alkyl oder -Alkoxy, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3, NO_2, C_1-C_4-Carbalkoxy, NR^7R^8 oder $NCOR^7$ ausgewählt

sind,

R^7 und R^8	unabhängig aus H oder C_1-C_4-Alkyl ausgewählt sind,
X	$S(O)_r$, O, NR^5, CH_2 ist,
A	C_2-C_{10}-Alkyl, verzweigtes C_3-C_{10}-Alkyl, C_3-C_{10}-Alkenyl oder C_3-C_{10}-Alkinyl ist,
Y	O, S, H_2 ist,
Z	NHR^4, OR^4 oder R^4 ist,
r	0-2 ist,

und gegebenenfalls das Bilden eines pharmazeutisch annehmbaren Salzes derselben.

12. Verfahren des Anspruchs **11**, das weiter das Entfernen einer etwaigen Schutzgruppe an R^3 umfaßt.

13. Verfahren des Anspruchs **11**, das weiter das Umsetzen einer Verbindung der Formel (I), worin Y O ist, mit Lawessons Reagenz oder Diphosphorpentasulfid unter Liefern einer Verbindung der Formel (I), worin Y S ist, umfaßt.

14. Verfahren des Anspruchs **11**, das weiter das Umsetzen einer Verbindung der Formel (I), worin Y O ist, mit einem Reduktionsmittel, wie etwa Lithiumaluminiumhydrid oder Natriumborhydrid, unter Liefern einer Verbindung der Formel (I), worin Y H_2 ist, umfaßt.

15. Verfahren des Anspruchs **11**, das weiter das Umsetzen einer Verbindung der Formel (I), worin X S ist, mit einem geeigneten Oxidationsmittel unter Liefern entweder des Sulfoxids SO, wobei r 1 ist, oder des Sulfons SO_2, wobei r 2 ist, umfaßt.

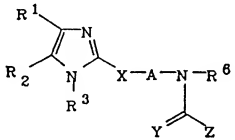
16. Verfahren des Anspruchs **11**, das weiter das Umsetzen einer Verbindung der Formel (I), worin R^3 H ist, mit einem geeigneten Alkylierungsmittel wie etwa einem Alkylhalogenid unter Liefern einer Verbindung der Formel (I), worin R^3 C_1-C_6-Alkyl, Allyl oder Benzyl ist, umfaßt.

17. Verfahren zum Herstellen einer pharmazeutischen Zusammensetzung umfassend das Mischen einer therapeutisch wirksamen Menge einer gemäß einem der Ansprüche 1 bis 16 hergestellten Verbindung und eines pharmazeutisch annehmbaren Trägers.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, GR, IT, LI, LU, NL, SE

1. Un composé de formule:



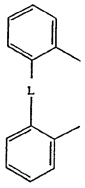
Formule (I)

dans laquelle:

R^1 et R^2 sont choisis, indépendamment l'un de l'autre, dans le groupe comprenant un atome d'hydrogène, un radical alkyle en C_1 à C_8, à condition que lorsque R^1 est un atome d'hydrogène, alors R^2 ne peut être un atome d'hydrogène et que lorsque R^1 est un radical alkyle en C_1 à C_8, alors R^2 ne peut pas être un radical alkyle en C_1 à C_8, un radical alkyle ramifié en C_3 à C_8, cycloalkyle en C_3 à C_7, cycloalkylalkyle en C_4 à C_{10}, aralkyle en C_7 à C_{14}, 2-, 3- ou 4-pyridinyle, 2-thiényle, 2-furanyle, phényle éventuelle-

ment substitué par 1 à 3 groupes sélectionnés parmi: atomes de fluor, chlore, brome, un groupe OH, un radical alcoxy en C_1 à C_4, alkyle en C_1 à C_4, alkyle ramifié en C_3 à C_8, $CH_3S(O)_t$, NO_2, CF_3 ou NR^7R^8; ou

R^1 et R^2 peuvent former ensemble un groupe:



dans lequel:

L est O, $O(CH_2)_{m+1}O$, ou $(CH_2)_m$, m étant un nombre de 0 à 4;

R^3 est un atome d'hydrogène, un radical alkyle en C_1 à C_6, allyle, benzyle ou phényle éventuellement substitué par un atome de fluor, de chlore, un groupe CH_3, CH_3O ou CF_3;

R^4 est un radical alkyle linéaire en C_1 à C_6 éventuellement substitué par un atome de fluor; un radical alkyle ramifié en C_3 à C_8, cycloalkyle en C_3 à C_7, cycloalkylalkyle en C_4 à C_{10}, aralkyle en C_7 à C_{14}, dans lequel le radical aryle est éventuellement substitué par un à trois groupes choisis parmi les radicaux alcoxy ou alkyle en C_1 à C_4, les atomes de fluor, brome, chlore, les groupes NH_2, OH, CN, CO_2H, CF_3, NO_2, carboalcoxy en C_1 à C_4, NR^7R^8 ou $NCOR^7$; les radicaux alkynyle ou alkényle en C_3 à C_6, perfluoroalkyle en C_1 à C_3, phényle éventuellement substitué par un groupe choisi parmi les radicaux alcoxy ou alkyle en C_1 à C_4, les atomes de fluor, brome, chlore, les groupes NH_2, OH, CN, CO_2H, CF_3, NO_2, les radicaux carboalcoxy en C_1 à C_4, NR^7R^8 ou $NCOR^7$; les radicaux pentafluorophényle, benzyle éventuellement substitué par 1 à 3 groupes choisis parmi les radicaux alcoxy ou alkyle en C_1 à C_4, les atomes de fluor, brome, chlore, les groupes NH_2, OH, CN, CO_2H, CF_3, NO_2, carboalcoxy en C_1 à C_4, NR^7R^8 ou $NCOR^7$; les radicaux 2-, 3- ou 4- pyridinyle, pyrimidinyle ou biphényle;

R^5 est un atome d'hydrogène ou un radical alkyle en C_1 à C_6 ou benzyle;

R^6 est un atome d'hydrogène, un radical alkyle en C_1 à C_8, alkyle ramifié en C_3 à C_8, cycloalkyle en C_3 à C_7, alkynyle ou alkényle en C_3 à C_8, phényle éventuellement substitué par 1 à 3 groupes choisis parmi les radicaux alcoxy ou alkyle en C_1 à C_4, les atomes de fluor, brome, chlore, les groupes NH_2, OH, CN, CO_2H, CF_3, NO_2, carboalcoxy en C_1 à C_4, NR^7R^8 ou $NCOR^7$; les radicaux pentafluorophényle, benzyle éventuellement substitué par 1 à 3 groupes choisi parmi les radicaux alcoxy ou alkyle en C_1 à C_4, les atomes de fluor, brome, chlore, les groupes NH_2, OH, CN, CO_2H, CF_3, NO_2, carboalcoxy en C_1 à C_4, NR^7R^8 ou $NCOR^7$;

R^7 et R^8 sont choisis, indépendamment l'un de l'autre, parmi l'atome d'hydrogène ou les radicaux alkyles en C_1 à C_4;

X est $S(O)_t$, O, NR^5, CH_2;

A est un radical alkyle en C_2 à C_{10}, alkyle ramifié en C_3 à C_{10}, alkényle en C_3 à C_{10}, ou alkynyle en C_3 à C_{10};

Y est O, S ou H_2;

Z est NHR^4, OR^4 ou R^4;

r est un nombre de 0 à 2,

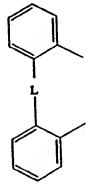
ou un sel pharmaceutiquement acceptable en dérivant.

2. Un composé selon la revendication 1, dans lequel:

R^1 et R^2 sont choisis, indépendamment l'un de l'autre, parmi les radicaux alkyles en C_1 à C_8, à

condition que lorsque R^1 est un radical alkyle en C_1 à C_8, R^2 ne puisse pas être un radical alkyle en C_1 à C_8, un radical alkyle ramifié en C_3 à C_8, cycloalkyle en C_3 à C_7, cycloalkylalkyle en C_4 à C_{10}, aralkyle en C_7 à C_{14}, 2-, 3- ou 4-pyridinyle, 2-thiényle, 2-furanyle, phényle éventuellement substitué par 1 ou 2 groupes choisis parmi F, Cl, Br, OH, alcoxy en C_1 à C_4, alkyle en C_1 à C_4, alkyle ramifié en C_3 à C_8, $CH_3S(O)_n$, NO_2, CF_3 ou NR^7R^8; ou encore

R^1 et R^2 peuvent former ensemble un groupe:



dans lequel:

L est O, $O(CH_2)_{m+1}O$, ou $(CH_2)_m$, m étant un nombre de 0 à 4.

3. Un composé selon la revendication 2, dans lequel:

R^3 est un atome d'hydrogène, un groupe CH_3, ou un groupe phényle;

R^6 est un atome d'hydrogène, un radical alkyle en C_1 à C_8, alkyle ramifié en C_3 à C_8, cycloalkyle en C_3 à C_7, phényle éventuellement substitué par 1 à 3 groupes choisis parmi CH_3, CH_3O, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3 ou dialkyl-(C_1 à C_4)-amino; ou benzyle éventuellement substitué par 1 à 3 groupes choisis parmi CH_3, CH_3O, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3 ou dialkyl-(C_1 à C_4)-amino;

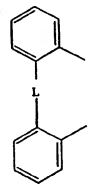
X est $S(O)_y$, CH_2;

A est un radical alkyle en C_2-C_{10}, ou alkyle ramifié en C_4- C_9.

4. Un composé selon la revendication 3, dans lequel:

R^1 et R^2 sont choisis, indépendamment l'un de l'autre, parmi les radicaux alkyle en C_1 à C_8, alkyle ramifié en C_3 à C_8, cycloalkyle en C_3 à C_7, cycloalkylalkyle en C_4 à C_{10}, aralkyle en C_7 à C_{14}, 2-, 3- ou 4-pyridinyle, 2-thiényle ou phényle éventuellement substitué par 1 ou 2 groupes choisis parmi F, Br, Cl, alkyle en C_1 à C_4, alkyle ramifié en C_3 à C_8, CH_3O, $CH_3S(O)_n$, NO_2, CF_3 ou dialkyl-(C_1 à C_4)-amino; ou

R^1 et R^2 peuvent former ensemble un groupe:



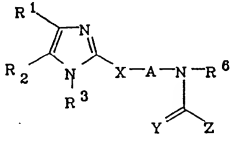
dans lequel:

L est 0 ou OCH_2O;
R^3 est un atome d'hydrogène;
R^4 est un radical alkyle en C_1 à C_8, alkyle ramifié en C_3 à C_8, cycloalkyle en C_3 à C_7, cycloalkylalkyle en C_4 à C_{10}, aralkyle en C_7 à C_{11}, phényle substitué par 1 à 3 groupes choisis parmi CH_3, F, Cl, CH_3O, CN, ou benzyle éventuellement substitué par 1 à 3 groupes choisis parmi CH_3, CH_3O, F, Cl ou CN;
R^6 est un radical alkyle en C_1 à C_8 ou phényle éventuellement substitué par 1 à 3 groupes choisis parmi CH_3, CH_3O, F, Cl ou CN;
A est un radical alkyle en C_4 à C_9;
X est $S(O)_x$;
Y est O, H_2.

5. Composé selon les revendications 1 à 4, choisi parmi ceux appartenant à la liste comprenant:
- N'-(2,4-difluorophényl)-N-[5-(4,5-diphényl-1H-imidazol-2-ylthio)pentyl]-N-heptylurée;
- N'-(2,4-difluorophényl)-N-[8-(4,5-diphényl-1H-imidazol-2-ylthio)octyl]-N-heptylurée;
- N-butyl-N'-(2,4-difluorophényl)-N-[8-(4,5-diphényl-1H-imidazol-2-ylthio)octyl]urée;
- N'-(2,4-diméthoxyphényl)-N-[5-(4,5-diphényl-1H-imidazol-2-ylthio)pentyl]-N-heptylurée;
- N-[5-(4,5-diphényl-1H-imidazol-2-ylthio)pentyl]-N-heptyl-N'-méthylurée;
- N-[5-(4,5-diphényl-1H-imidazol-2-ylthio)pentyl]-N-heptyl-N'-propylurée;
- N-[5-(4,5-diphényl-1H-imidazol-2-ylthio)pentyl]-N'-(3-fluorophényl)-N-heptylurée;
- N'-(2,4-difluorophényl)-N-[5-[(4,5-diphényl-1H-imidazol-2-yl)sulfonyl]pentyl]-N-heptylurée;
- N-[5-(4,5-diphényl-1H-imidazol-2-ylthio)pentyl]-N-heptyl-N'-(1-méthyléthyl)urée;
- N-[5-(4,5-diphényl-1H-imidazol-2-ylthio)pentyl]-N-2,4-difluoro-N-heptylbenzèneacétamide;
- N'-cyclohexyl-N-[5-(4,5-diphényl-1H-imidazol-2-ylthio)pentyl]-N-heptylurée;
- N'-(2,4-difluorophényl)-N-[5-([4,5-diphényl-1H-imidazol-2-yl)sulfinyl]pentyl]-N-heptylurée;
- N-[5-(4,5-diphényl-1H-imidazol-2-ylthio)pentyl]-N-heptylbutanamide;
- N-[5-[4,5-bis(1-méthyléthyl)-1H-imidazol-2-ylthio]pentyl]-N'-(2,4-difluorophényl)-N-heptylurée;
- N-[5-[4,5-bis(1-méthyléthyl)-1H-imidazol-2-ylthio]pentyl]-N-heptylcyclohexaneacétamide;
- N-[5-[4,5-bis(2-méthoxyphényl)-1H-imidazol-2-ylthio]pentyl]-N'-(2,4-difluorophényl)-N-heptylurée;
- Phényl-[5-(4,5-diphényl-1H-imidazol-2-ylthio)pentyl]heptylcarbamate;
- N-[5-[4,5-bis[4-(diméthylamino)phényl]-1H-imidazol-2-ylthio]pentyl]-N'-(2,4-difluorophényl)-N-heptylurée;
- N-[5-(4,5-diphényl-1H-imidazol-2-ylthio)pentyl]-N'-octyl-N-phénylurée;
- N-[5-[4,5-bis(4-méthoxyphényl)-1H-imidazol-2-ylthio]pentyl]-2,4-difluoro-N-heptylbenzèneacétamide;
- Phényl-[5-[(4,5-bis-(4-diméthylamino)phényl)-1H-imidazol-2-ylthio]pentyl]-heptylcarbamate; et
- N-[5-(4,5-dicyclohexyl-1H-imidazol-2-ylthio)pentyl]-N'-(2,4-difluorophényl)-N-heptylurée.

6. Une composition pharmaceutique comprenant une quantité efficace du point de vue thérapeutique d'un composé selon une des revendications 1 à 5 ainsi qu'un support pharmaceutiquement acceptable.

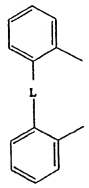
7. Un procédé de préparation d'un composé de formule (I):



dans laquelle:
R^1 et R^2 sont choisis, indépendamment l'un de l'autre, dans le groupe comprenant un atome d'hydrogène, un radical alkyle en C_1 à C_8, à condition que lorsque R^1 est un atome

d'hydrogène, alors R^2 ne peut être un atome d'hydrogène et que lorsque R^1 est un radical alkyle en C_1 à C_8, alors R^2 ne peut pas être un radical alkyle en C_1 à C_8, un radical alkyle ramifié en C_3 à C_8, cycloalkyle en C_3 à C_7, cycloalkylalkyle en C_4 à C_{10}, aralkyle en C_7 à C_{14}, 2-, 3- ou 4-pyridinyle, 2-thiényle, 2-furanyle, phényle éventuellement substitué par 1 à 3 groupes sélectionnés parmi: atomes de fluor, chlore, brome, un groupe OH, un radical alcoxy en C_1 à C_4, alkyle en C_1 à C_4, alkyle ramifié en C_3 à C_6, $CH_3S(O)_r$, NO_2, CF_3 ou NR^7R^8; ou

R^1 et R^2 peuvent former ensemble un groupe:



dans lequel:

L est O, $O(CH_2)_{m+1}O$, ou $(CH_2)_m$, m étant un nombre de 0 à 4;

R^3 est un atome d'hydrogène, un radical alkyle en C_1 à C_6, allyle, benzyle ou phényle éventuellement substitué par un atome de fluor, de chlore, un groupe CH_3, CH_3O ou CF_3;

R^4 est un radical alkyle linéaire en C_1 à C_8 éventuellement substitué par un atome de fluor; un radical alkyle ramifié en C_3 à C_8, cycloalkyle en C_3 à C_7, cycloalkylalkyle en C_4 à C_{10}, aralkyle en C_7 à C_{14}, dans lequel le radical aryle est éventuellement substitué par un à trois groupes choisis parmi les radicaux alcoxy ou alkyle en C_1 à C_4, les atomes de fluor, brome, chlore, les groupes NH_2, OH, CN, CO_2H, CF_3, NO_2, carboalcoxy en C_1 à C_4, NR^7R^8 ou $NCOR^7$; les radicaux alkynyle ou alkényle en C_3 à C_6, perfluoroalkyle en C_1 à C_3, phényle éventuellement substitué par un groupe choisi parmi les radicaux alcoxy ou alkyle en C_1 à C_4, les atomes de fluor, brome, chlore, les groupes NH_2, OH, CN, CO_2H, CF_3, NO_2, les radicaux carboalcoxy en C_1 à C_4, NR^7R^8 ou $NCOR^7$; les radicaux pentafluorophényle, benzyle éventuellement substitué par 1 à 3 groupes choisis parmi les radicaux alcoxy ou alkyle en C_1 à C_4, les atomes de fluor, brome, chlore, les groupes NH_2, OH, CN, CO_2H, CF_3, NO_2, carboalcoxy en C_1 à C_4, NR^7R^8 ou $NCOR^7$; les radicaux 2-, 3- ou 4-pyridinyle, pyrimidinyle ou biphényle;

R^5 est un atome d'hydrogène ou un radical alkyle en C_1 à C_5 ou benzyle;

R^6 est un atome d'hydrogène, un radical alkyle en C_1 à C_8, alkyle ramifié en C_3 à C_8, cycloalkyle en C_3 à C_7, alkynyle ou alkényle en C_3 à C_8, phényle éventuellement substitué par 1 à 3 groupes choisis parmi les radicaux alcoxy ou alkyle en C_1 à C_4, les atomes de fluor, brome, chlore, les groupes NH_2, OH, CN, CO_2H, CF_3, NO_2, carboalcoxy en C_1 à C_4, NR^7R^8 ou $NCOR^7$; les radicaux pentafluorophényle, benzyle éventuellement substitué par 1 à 3 groupes choisi parmi les radicaux alcoxy ou alkyle en C_1 à C_4, les atomes de fluor, brome, chlore, les groupes NH_2, OH, CN, CO_2H, CF_3, NO_2, carboalcoxy en C_1 à C_4, NR^7R^8 ou $NCOR^7$;

R^7 et R^8 sont choisis, indépendamment l'un de l'autre, parmi l'atome d'hydrogène ou les radicaux alkyles en C_1 à C_4;

X est $S(O)_t$, O, NR^5, CH_2;

A est un radical alkyle en C_2 à C_{10}, alkyle ramifié en C_3 à C_{10}, alkényle en C_2 à C_{10}, ou alkynyle en C_3 à C_{10};

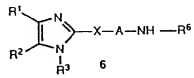
Y est O, S ou H_2;

Z est NHR^4, OR^4 ou R^4;

r est un nombre de 0 à 2,

ou un sel pharmaceutiquement acceptable en dérivant; comprenant les étapes de:

- réaction d'un composé de formule:



6

dans laquelle:

R^1, R^2, X, A et R^6	sont tels que définis ci-dessus; et
R^3	est également tel que défini ci-dessus, ou est un groupe protecteur convenable tel qu'un groupe silyle ou trilyle,

avec:

i) un isocyanate de formule:

$R^4\text{-}N=C=O$

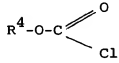
dans laquelle R^4 est tel que défini ci-dessus, pour conduire à un composé représenté par la formule (I) décrite ci-dessus, dans laquelle Y représente O et Z est NHR^4; ou

ii) un isothiocyanate de formule:

$R^4\text{-}N=C=S$

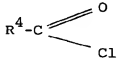
dans laquelle R^4 est tel que défini ci-dessus, pour conduire à un composé représenté par la formule (I) décrite ci-dessus, dans laquelle Y est S et Z est NHR^4; ou

iii) un chloroformiate de formule:



dans laquelle R^4 est tel que défini ci-dessus, pour conduire à un composé représenté par la formule (I) décrite ci-dessus, dans laquelle Y représente O et Z est OR^4; ou

iv) un chlorure d'acide de formule:



ou un autre acide carboxylique activé, dans laquelle R^4 est tel que défini ci-dessus, pour conduire à un composé représenté par la formule (I) décrite ci-dessus, dans laquelle Y représente O et Z est R^4.

8. Un procédé selon la revendication 7, comprenant en outre l'élimination de tout groupe protecteur sur R^3 pour conduire à un composé de formule (I) dans laquelle R^3 est H.

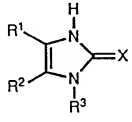
9. Un procédé selon la revendication 7, comprenant en outre la réaction d'un composé de formule (I) dans laquelle Y est O, avec un réactif de Lawesson ou un pentasulfure diphosphoreux, pour conduire à un composé de formule (I) dans laquelle Y est S.

10. Un procédé selon la revendication 7, comprenant en outre la réaction d'un composé de formule (I) dans laquelle Y est O, avec un agent réducteur tel que l'hydrure d'aluminium lithium ou du borohydrure de sodium, pour conduire à un composé de formule (I) dans laquelle Y est H_2.

11. Un procédé selon la revendication 7, comprenant en outre la réaction d'un composé de formule (I) dans laquelle X est S, avec un agent d'oxydation convenable pour obtenir soit le sulfoxyde SO, dans lequel r est égal à 1, soit la sulfone SO_2, dans lequel r est égal à 2.

12. Un procédé selon la revendication 7, comprenant en outre la réaction d'un composé de formule (I) dans laquelle R^3 est un atome d'hydrogène, avec un agent d'alkylation convenable tel qu'un halogénure d'alkyle, pour conduire à l'obtention d'un composé de formule (I) dans laquelle R^3 est un radical alkyle en C_1 à C_6, allyle ou benzyle.

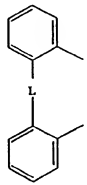
13. Un procédé comprenant les étapes d'alkylation d'un composé de formule:



dans laquelle:

R^1 et R^2 sont choisis, indépendamment l'un de l'autre, le groupe comprenant un atome d'hydrogène, un radical alkyle en C_1 à C_8, à condition que lorsque R^1 est un atome d'hydrogène, alors R^2 ne peut être un atome d'hydrogène et que lorsque R^1 est un radical alkyle en C_1 à C_8, alors R^2 ne peut pas être un radical alkyle en C_1 à C_8, un radical alkyle ramifié en C_3 à C_8, cycloalkyle en C_3 à C_7, cycloalkylalkyle en C_4 à C_{10}, aralkyle en C_7 à C_{14}, 2-, 3- ou 4-pyridinyle, 2-thiényle, 2-furanyle, phényle éventuellement substitué par 1 à 3 groupes sélectionnés parmi: atomes de fluor, chlore, brome, un groupe OH, un radical alcoxy en C_1 à C_4, alkyle en C_1 à C_4, alkyle ramifié en C_3 à C_8, $CH_3S(O)_n$, NO_2, CF_3 ou NR^7R^8; ou

R^1 et R^2 peuvent former ensemble un groupe:



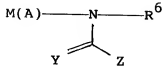
dans lequel:

L est O, $O(CH_2)_{m+1}O$, ou $(CH_2)_m$, m étant un nombre de 0 à 4;

R^3 est un atome d'hydrogène, un radical alkyle en C_1 à C_6, allyle, benzyle ou phényle éventuellement substitué par un atome de fluor, de chlore, un groupe CH_3, CH_3O ou CF_3; ou un groupe protecteur convenable tel qu'un groupe silyle ou trilyle; et

X est O ou S,

avec un composé de formule:



dans laquelle:

M est un halogénure ou un tosylate;

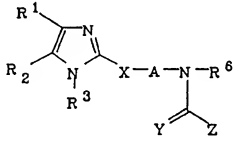
A est un radical alkyle en C_2 à C_{10}, alkyle ramifié en C_3 à C_{10}, alkényle en C_3 à C_{10}, ou alkynyle en C_3 à C_{10};

R^6 est un atome d'hydrogène, un radical alkyle en C_1 à C_8, alkyle ramifié en C_3 à C_8, cycloalkyle en C_3 à C_7, alkynyle ou alkényle en C_3 à C_8, phényle éventuellement substitué par 1 à 3 groupes choisis parmi alcoxy ou alkyle en C_1 à C_4, les atomes de fluor, brome, chlore, les groupes NH_2, OH, CN, CO_2H, CF_3, NO_2, carboalcoxy en C_1 à C_4, NR^7R^8 ou $NCOR^7$; pentafluorophényle, benzyle éventuellement substitué par 1 à 3 groupes choisi parmi alcoxy ou alkyle en C_1 à C_4, les atomes de fluor, brome, chlore, les groupes NH_2, OH, CN, CO_2H, CF_3, NO_2, carboalcoxy en C_1 à C_4, NR^7R^8 ou $NCOR^7$;

Y est O, S ou H_2; et

Z est NHR^4, OR^4 ou R^4,

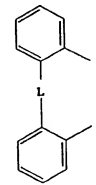
pour conduire à un composé de formule (I):



dans laquelle:

R^1 et R^2 sont choisis, indépendamment l'un de l'autre, dans le groupe comprenant un atome d'hydrogène, un radical alkyle en C_1 à C_8, alkyle ramifié en C_3 à C_8, cycloalkyle en C_3 à C_7, cycloalkylalkyle en C_4 à C_{10}, aralkyle en C_7 à C_{14}, 2-, 3- ou 4-pyridinyle, 2-thiényle, 2-furanyle, phényle éventuellement substitué par 1 à 3 groupes sélectionnés parmi: atomes de fluor, chlore, brome, groupe OH, radical alcoxy en C_1 à C_4, alkyle en C_1 à C_4, alkyle ramifié en C_3 à C_8, $CH_3S(O)_n$, NO_2, CF_3 ou NR^7R^8; ou

R^1 et R^2 peuvent former ensemble un groupe:



dans lequel:

L est O, $O(CH_2)_{m+1}O$, ou $(CH_2)_m$, m étant un nombre de 0 à 4;

R^3 est un atome d'hydrogène, un radical alkyle en C_1 à C_6, allyle, benzyle ou phényle éventuellement substitué par un atome de fluor, de chlore, un groupe CH_3, CH_3O ou CF_3;

R^4 est un radical alkyle linéaire en C_1 à C_8 éventuellement substitué par un atome de fluor; un radical alkyle ramifié en C_3 à C_8, cycloalkyle en C_3 à C_7, cycloalkylalkyle en C_4 à C_{10}, aralkyle en C_7 à C_{14}, dans lequel le radical aryle est éventuellement substitué par un à trois groupes choisis parmi les radicaux alcoxy ou alkyle en C_1 à C_4, les atomes de fluor, brome, chlore, les groupes NH_2, OH, CN, CO_2H, CF_3, NO_2, carboalcoxy en C_1 à C_4, NR^7R^8 ou $NCOR^7$; les radicaux alkynyle ou alkényle en C_3 à C_6, perfluoroalkyle en C_1 à C_3, phényle éventuellement substitué par un groupe choisi parmi les radicaux alcoxy ou alkyle en C_1 à C_4, les atomes de fluor, brome, chlore, les groupes NH_2, OH, CN, CO_2H, CF_3, NO_2, les radicaux carboalcoxy en C_1 à C_4, NR^7R^8 ou $NCOR^7$; les radicaux pentafluorophényle, benzyle éventuellement substitué par 1 à 3 groupes choisis parmi les radicaux alcoxy ou alkyle en C_1 à C_4, les atomes de fluor, brome, chlore, les groupes NH_2, OH, CN, CO_2H, CF_3, NO_2, carboalcoxy en C_1 à C_4, NR^7R^8 ou $NCOR^7$; les radicaux 2-, 3- ou 4-pyridinyle, pyrimidinyle ou biphényle;

R^5 est un atome d'hydrogène ou un radical alkyle en C_1 à C_6 ou benzyle;

R^6 est un atome d'hydrogène, un radical alkyle en C_1 à C_8, alkyle ramifié en C_3 à C_8, cycloalkyle en C_3 à C_7, alkynyle ou alkényle en C_3 à C_8, phényle éventuellement substitué par 1 à 3 groupes choisis parmi les radicaux alcoxy ou alkyle en C_1 à C_4, les atomes de fluor, brome, chlore, les groupes NH_2, OH, CN, CO_2H, CF_3, NO_2, carboalcoxy en C_1 à C_4, NR^7R^8 ou $NCOR^7$; les radicaux pentafluorophényle, benzyle éventuellement substitué par 1 à 3 groupes choisi parmi les radicaux alcoxy ou alkyle en C_1 à C_4, les atomes de fluor, brome, chlore, les groupes NH_2, OH, CN, CO_2H, CF_3, NO_2, carboalcoxy en C_1 à C_4, NR^7R^8 ou $NCOR^7$;

R^7 et R^8 sont, indépendamment l'un de l'autre, choisis parmi l'atome d'hydrogène ou les radicaux alkyles en C_1 à C_4;

X est $S(O)_r$, O, NR^5, CH_2;

A est un radical alkyle en C_2 à C_{10}, alkyle ramifié en C_3 à C_{10}, alkényle en C_3 à C_{10}, ou alkynyle en C_3 à C_{10};

Y est O, S ou H_2;

Z est NHR^4, OR^4 ou R^4;

r est un nombre de 0 à 2,

et formant éventuellement un sel pharmaceutiquement acceptable en dérivant.

14. Un procédé selon la revendication 13, comprenant en outre l'élimination de tout groupe protecteur sur R^3.

15. Un procédé selon la revendication 13, comprenant en outre la réaction d'un composé de formule (I) dans laquelle Y est O, avec un réactif de Lawesson ou un pentasulfure diphosphoreux, pour conduire à un composé de formule (I) dans laquelle Y est S.

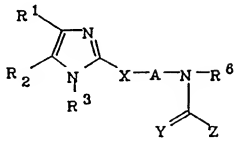
16. Un procédé selon la revendication 13, comprenant en outre la réaction d'un composé de formule (I) dans laquelle Y est O, avec un agent réducteur tel que l'hydrure d'aluminium lithium ou du borohydrure de sodium, pour conduire à un composé de formule (I) dans laquelle Y est H_2.

17. Un procédé selon la revendication 13, comprenant en outre la réaction d'un composé de formule (I) dans laquelle X est S, avec un agent d'oxydation convenable pour obtenir soit le sulfoxyde SO, dans lequel r est égal à 1, soit la sulfone SO_2, dans laquelle r est égal à 2.

18. Un procédé selon la revendication 13, comprenant en outre la réaction d'un composé de formule (I) dans laquelle R^3 est un atome d'hydrogène, avec un agent d'alkylation convenable tel qu'un halogénure d'alkyle, pour conduire à l'obtention d'un composé de formule (I) dans laquelle R^3 est un radical alkyle en C_1 à C_6, allyle ou benzyle.

Revendications pour l'Etat contractant suivant : ES

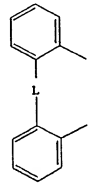
1. Un procédé de préparation d'un composé de formule (I):



dans laquelle:

R^1 et R^2 sont choisis, indépendamment l'un de l'autre, dans le groupe comprenant un atome d'hydrogène, un radical alkyle en C_1 à C_8, à condition que lorsque R^1 est un atome d'hydrogène, alors R^2 ne peut être un atome d'hydrogène et que lorsque R^1 est un radical alkyle en C_1 à C_8, alors R^2 ne peut pas être un radical alkyle en C_1 à C_8, un radical alkyle ramifié en C_3 à C_8, cycloalkyle en C_3 à C_7, cycloalkylalkyle en C_4 à C_{10}, aralkyle en C_7 à C_{14}, 2-, 3- ou 4-pyridinyle, 2-thiényle, 2-furanyle, phényle éventuellement substitué par 1 à 3 groupes sélectionnés parmi: atomes de fluor, chlore, brome, un groupe OH, un radical alcoxy en C_1 à C_4, alkyle en C_1 à C_4, alkyle ramifié en C_3 à C_8, $CH_3S(O)_n$, NO_2, CF_3 ou NR^7R^8; ou

R^1 et R^2 peuvent former ensemble un groupe:



dans lequel:

L est O, $O(CH_2)_{m+1}O$, ou $(CH_2)_m$, m étant un nombre de 0 à 4;

R^3 est un atome d'hydrogène, un radical alkyle en C_1 à C_5, allyle, benzyle ou phényle éventuellement substitué par un atome de fluor, de chlore, un groupe CH_3, CH_3O ou CF_3;

R^4 est un radical alkyle linéaire en C_1 à C_8 éventuellement substitué par un atome de fluor; un radical alkyle ramifié en C_3 à C_8, cycloalkyle en C_3 à C_7, cycloalkylalkyle en C_4 à C_{10}, aralkyle en C_7 à C_{14}, dans lequel le radical aryle est éventuellement substitué par un à trois groupes choisis parmi les radicaux alcoxy ou alkyle en C_1 à C_4, les atomes de fluor, brome, chlore, les groupes NH_2, OH, CN, CO_2H, CF_3, NO_2, carboalcoxy en C_1 à C_4 NR^7R^8 ou $NCOR^7$; les radicaux alkynyle ou alkényle en C_3 à C_5, perfluoroalkyle en C_1 à C_3, phényle éventuellement substitué par un groupe choisi parmi les radicaux alcoxy ou alkyle en C_1 à C_4, les atomes de fluor, brome, chlore, les groupes NH_2, OH, CN, CO_2H, CF_3, NO_2, les radicaux carboalcoxy en C_1 à C_4, NR^7R^8 ou $NCOR^7$; les radicaux pentafluorophényle, benzyle éventuellement substitué par 1 à 3 groupes choisis parmi les radicaux alcoxy ou alkyle en C_1 à C_4, les atomes de fluor,

brome, chlore, les groupes NH_2, OH, CN, CO_2H, CF_3, NO_2, carboalcoxy en C_1 à C_4, NR^7R^8 ou $NCOR^7$; les radicaux 2-, 3- ou 4-pyridinyle, pyrimidinyle ou biphényle;

R^5 est un atome d'hydrogène ou un radical alkyle en C_1 à C_6 ou benzyle;

R^6 est un atome d'hydrogène, un radical alkyle en C_1 à C_8, alkyle ramifié en C_3 à C_8, cycloalkyle en C_3 à C_7, alkynyle ou alkényle en C_3 à C_8, phényle éventuellement substitué par 1 à 3 groupes choisis parmi les radicaux alcoxy ou alkyle en C_1 à C_4, les atomes de fluor, brome, chlore, les groupes NH_2, OH, CN, CO_2H, CF_3, NO_2, carboalcoxy en C_1 à C_4, NR^7R^8 ou $NCOR^7$; les radicaux pentafluorophényle, benzyle éventuellement substitué par 1 à 3 groupes choisi parmi les radicaux alcoxy ou alkyle en C_1 à C_4, les atomes de fluor, brome, chlore, les groupes NH_2, OH, CN, CO_2H, CF_3, NO_2, carboalcoxy en C_1 à C_4, NR^7R^8 ou $NCOR^7$;

R^7 et R^8 sont choisis, indépendamment l'un de l'autre, parmi l'atome d'hydrogène ou les radicaux alkyles en C_1 à C_4;

X est $S(O)_n$, O, NR^5, CH_2;

A est un radical alkyle en C_2 à C_{10}, alkyle ramifié en C_3 à C_{10}, alkényle en C_3 à C_{10}, ou alkynyle en C_3 à C_{10};

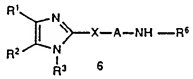
Y est O, S ou H_2;

Z est NHR^4, OR^4 ou R^4;

r est un nombre de 0 à 2,

ou un sel pharmaceutiquement acceptable en dérivant; comprenant les étapes de:

- réaction d'un composé de formule:



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dans laquelle:

R^1, R^2, X, A et R^6 sont tels que définis ci-dessus; et

R^3 est également tel que défini ci-dessus, ou est un groupe protecteur convenable tel qu'un groupe silyle ou trilyle,

avec:

i) un isocyanate de formule:

$R^4\text{-}N=C=O$

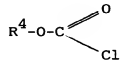
dans laquelle R^4 est tel que défini ci-dessus, pour conduire à un composé représenté par la formule (I) décrite ci-dessus, dans laquelle Y représente O et Z est NHR^4; ou

ii) un isothiocyanate de formule:

$R^4\text{-}N=C=S$

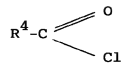
dans laquelle R^4 est tel que défini ci-dessus, pour conduire à un composé représenté par la formule (I) décrite ci-dessus, dans laquelle Y est S et Z est NHR^4; ou

iii) un chloroformiate de formule:



dans laquelle R^4 est tel que défini ci-dessus, pour conduire à un composé représenté par la formule (I) décrite ci-dessus, dans laquelle Y représente O et Z est OR^4; ou

iv) un chlorure d'acide de formule:

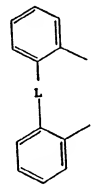


ou un autre acide carboxylique activé, dans laquelle R^4 est tel que défini ci-dessus, pour conduire à un composé représenté par la formule (I) décrite ci-dessus, dans laquelle Y représente O et Z est R^4.

2. Un procédé selon la revendication 1, dans lequel:

R^1 et R^2 sont choisis, indépendamment l'un de l'autre, parmi les radicaux alkyles en C_1 à C_8, à condition que lorsque R^1 est un radical alkyle en C_1 à C_8, R^2 ne puisse pas être un radical alkyle en C_1 à C_8, un radical alkyle ramifié en C_3 à C_8, cycloalkyle en C_3 à C_7, cycloalkylalkyle en C_4 à C_{10}, aralkyle en C_7 à C_{14}, 2-, 3- ou 4-pyridinyle, 2-thiényle, 2-furanyle, phényle éventuellement substitué par 1 ou 2 groupes choisis parmi F, Cl, Br, OH, alcoxy en C_1 à C_4, alkyle en C_1 à C_4, alkyle ramifié en C_3 à C_8, $CH_3S(O)_r$, NO_2, CF_3 ou NR^7R^8; ou encore

R^1 et R^2 peuvent former ensemble un groupe:



dans lequel:

L est O, $O(CH_2)_{m+1}O$, ou $(CH_2)_m$, m étant un nombre de 0 à 4.

3. Un procédé selon la revendication 2, dans lequel:

R^3 est un atome d'hydrogène, un groupe CH_3, ou un groupe phényle;

R^6 est un atome d'hydrogène, un radical alkyle en C_1 à C_8, alkyle ramifié en C_3 à C_8, cycloalkyle en C_3 à C_7, phényle éventuellement substitué par 1 à 3 groupes choisis parmi CH_3, CH_3O, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3 ou dialkyl-(C_1 à C_4)-amino; ou benzyle éventuellement substitué par 1 à 3 groupes choisis parmi CH_3, CH_3O, F, Br, Cl, NH_2, OH, CN, CO_2H, CF_3 ou dialkyl-(C_1 à C_4)-amino;

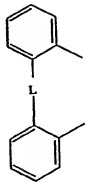
X est $S(O)_r$, CH_2;

A est un radical alkyle en C_2-C_{10}, ou alkyle ramifié en C_4- C_9.

4. Un procédé selon la revendication 3, dans lequel:

R^1 et R^2 sont choisis, indépendamment l'un de l'autre, parmi les radicaux alkyle en C_1 à C_8, alkyle ramifié en C_3 à C_8, cycloalkyle en C_3 à C_7, cycloalkylalkyle en C_4 à C_{10}, aralkyle en C_7 à C_{14}, 2-, 3- ou 4-pyridinyle, 2-thiényle ou phényle éventuellement substitué par 1 ou 2 groupes choisis parmi F, Br, Cl, alkyle en C_1 à C_4, alkyle ramifié en C_3 à C_8, CH_3O, $CH_3S(O)_r$, NO_2, CF_3 ou dialkyl-(C_1 à C_4)-amino; ou

R^1 et R^2 peuvent former ensemble un groupe:



dans lequel:

L	est 0 ou OCH_2O;
R^3	est un atome d'hydrogène;
R^4	est un radical alkyle en C_1 à C_8, alkyle ramifié en C_3 à C_8, cycloalkyle en C_3 à C_7, cycloalkylalkyle en C_4 à C_{10}, aralkyle en C_7 à C_{14}, phényle substitué par 1 à 3 groupes choisis parmi CH_3, F, Cl, CH_3O, CN, ou benzyle éventuellement substitué par 1 à 3 groupes choisis parmi CH_3, CH_3O, F, Cl ou CN;
R^6	est un radical alkyle en C_1 à C_8 ou phényle éventuellement substitué par 1 à 3 groupes choisis parmi CH_3, CH_3O, F, Cl ou CN;
A	est un radical alkyle en C_4 à C_9;
X	est $S(O)_r$;
Y	est O, H_2.

5. Un procédé selon les revendications 1 à 4, dans lequel les composés sont choisis parmi ceux appartenant à la liste comprenant:

- N'-(2,4-difluorophényl)-N-[5-(4,5-diphényl-1H-imidazol-2-ylthio)pentyl]-N-heptylurée;
- N'-(2,4-difluorophényl)-N-[8-(4,5-diphényl-1H-imidazol-2-ylthio)octyl]-N-heptylurée;
- N-butyl-N'-(2,4-difluorophényl)-N-[8-(4,5-diphényl-1H-imidazol-2-ylthio)octyl]urée;
- N'-(2,4-diméthoxyphényl)-N-[5-(4,5-diphényl-1H-imidazol-2-ylthio)pentyl]-N-heptylurée;
- N-[5-(4,5-diphényl-1H-imidazol-2-ylthio)pentyl]-N-heptyl-N'-méthylurée;
- N-[5-(4,5-diphényl-1H-imidazol-2-ylthio)pentyl]-N-heptyl-N'-propylurée;
- N-[5-(4,5-diphényl-1H-imidazol-2-ylthio)pentyl]-N'-(3-fluorophényl)-N-heptylurée;
- N'-(2,4-difluorophényl)-N-[5-[(4,5-diphényl-1H-imidazol-2-yl)sulfonyl)pentyl]-N-heptylurée;
- N-[5-(4,5-diphényl-1H-imidazol-2-ylthio)pentyl]-N-heptyl-N'-(1-méthyléthyl)urée;
- N-[5-(4,5-diphényl-1H-imidazol-2-ylthio)pentyl]-N-2,4-difluoro-N-heptylbenzèneacétamide;
- N'-cyclohexyl-N-[5-(4,5-diphényl-1H-imidazol-2-ylthio)pentyl]-N-heptylurée;
- N'-(2,4-difluorophényl)-N-[5-([4,5-diphényl-1H-imidazol-2-yl)sulfinyl]pentyl]-N-heptylurée;
- N-[5-(4,5-diphényl-1H-imidazol-2-ylthio)pentyl]-N-heptylbutanamide;
- N-[5-[4,5-bis(1-méthyléthyl)-1H-imidazol-2-ylthio]pentyl]-N'-(2,4-difluorophényl)-N-heptylurée;
- N-[5-[4,5-bis(1-méthyléthyl)-1H-imidazol-2-ylthio]pentyl]-N-heptylcyclohexaneacétamide;
- N-[5-[4,5-bis(2-méthoxyphényl)-1H-imidazol-2-ylthio]pentyl]-N'-(2,4-difluorophényl)-N-heptylurée;
- Phényl-[5-(4,5-diphényl-1H-imidazol-2-ylthio)pentyl]heptylcarbamate;
- N-[5-[4,5-bis[4-(diméthylamino)phényl]-1H-imidazol-2-ylthio]pentyl]-N'-(2,4-difluorophényl)-N-heptylurée;
- N-[5-(4,5-diphényl-1H-imidazol-2-ylthio)pentyl]-N'-octyl-N-phénylurée;
- N-[5-[4,5-bis(4-méthoxyphényl)-1H-imidazol-2-ylthio]pentyl]-2,4-difluoro-N-heptylbenzèneacétamide;
- Phényl-[5-[(4,5-bis-(4-diméthylamino)phényl)-1H-imidazol-2-ylthio]pentyl]-heptylcarbamate; et
- N-[5-(4,5-dicyclohexyl-1H-imidazol-2-ylthio)pentyl]-N'-(2,4-difluorophényl)-N-heptylurée.

6. Un procédé selon la revendication 1, comprenant en outre l'élimination de tout groupe protecteur sur R^3 pour conduire à un composé de formule (I) dans laquelle R^3 est H.

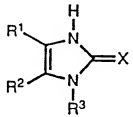
7. Un procédé selon la revendication 1, comprenant en outre la réaction d'un composé de formule (I) dans laquelle Y est O, avec un réactif de Lawesson ou un pentasulfure diphosphoreux, pour conduire à un composé de formule (I) dans laquelle Y est S.

8. Un procédé selon la revendication 1, comprenant en outre la réaction d'un composé de formule (I) dans laquelle Y est O, avec un agent réducteur tel que l'hydrure d'aluminium lithium ou du borohydrure de sodium, pour conduire à un composé de formule (I) dans laquelle Y est H_2.

9. Un procédé selon la revendication 1, comprenant en outre la réaction d'un composé de formule (I) dans laquelle X est S, avec un agent d'oxydation convenable pour obtenir soit le sulfoxyde SO, dans lequel r est égal à 1, soit la sulfone SO_2, dans laquelle r est égal à 2.

10. Un procédé selon la revendication 1, comprenant en outre la réaction d'un composé de formule (I) dans laquelle R^3 est un atome d'hydrogène, avec un agent d'alkylation convenable tel qu'un halogénure d'alkyle, pour conduire à l'obtention d'un composé de formule (I) dans laquelle R^3 est un radical alkyle en C_1 à C_6, allyle ou benzyle.

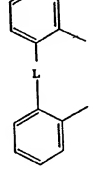
11. Un procédé comprenant les étapes d'alkylation d'un composé de formule:



dans laquelle:

R^1 et R^2 sont choisis, indépendamment l'un de l'autre, le groupe comprenant un atome d'hydrogène, un radical alkyle en C_1 à C_8, à condition que lorsque R^1 est un atome d'hydrogène, alors R^2 ne peut être un atome d'hydrogène et que lorsque R^1 est un radical alkyle en C_1 à C_8, alors R^2 ne peut pas être un radical alkyle en C_1 à C_8, un radical alkyle ramifié en C_3 à C_8, cycloalkyle en C_3 à C_7, cycloalkylalkyle en C_4 à C_{10}, aralkyle en C_7 à C_{14}, 2-, 3- ou 4-pyridinyle, 2-thiényle, 2-furanyle, phényle éventuellement substitué par 1 à 3 groupes sélectionnés parmi: atomes de fluor, chlore, brome, un groupe OH, un radical alcoxy en C_1 à C_4, alkyle en C_1 à C_4, alkyle ramifié en C_3 à C_8, $CH_3S(O)_n$, NO_2, CF_3 ou NR^7R^8; ou

R^1 et R^2 peuvent former ensemble un groupe:



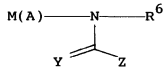
dans lequel:

L est O, $O(CH_2)_{m+1}O$, ou $(CH_2)_m$, m étant un nombre de 0 à 4;

R^3 est un atome d'hydrogène, un radical alkyle en C_1 à C_6, allyle, benzyle ou phényle éventuellement substitué par un atome de fluor, de chlore, un groupe CH_3, CH_3O ou CF_3; ou un groupe protecteur convenable tel qu'un groupe silyle ou trilyle; et

X est O ou S,

avec un composé de formule:



dans laquelle:

M est un halogénure ou un tosylate;

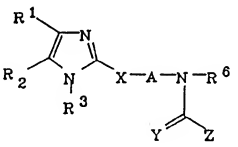
A est un radical alkyle en C_2 à C_{10}, alkyle ramifié en C_3 à C_{10}, alkényle en C_3 à C_{10}, ou alkynyle en C_3 à C_{10};

R^6 est un atome d'hydrogène, un radical alkyle en C_1 à C_8, alkyle ramifié en C_3 à C_8, cycloalkyle en C_3 à C_7, alkynyle ou alkényle en C_3 à C_8, phényle éventuellement substitué par 1 à 3 groupes choisis parmi alcoxy ou alkyle en C_1 à C_4, les atomes de fluor, brome, chlore, les groupes NH_2, OH, CN, CO_2H, CF_3, NO_2, carboalcoxy en C_1 à C_4, NR^7R^8 ou $NCOR^7$; pentafluorophényle, benzyle éventuellement substitué par 1 à 3 groupes choisi parmi alcoxy ou alkyle en C_1 à C_4, les atomes de fluor, brome, chlore, les groupes NH_2, OH, CN, CO_2H, CF_3, NO_2, carboalcoxy en C_1 à C_4, NR^7R^8 ou $NCOR^7$;

Y est O, S ou H_2; et

Z est NHR^4, OR^4 ou R^4,

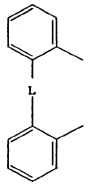
pour conduire à un composé de formule (I):



dans laquelle:

R^1 et R^2 sont choisis, indépendamment l'un de l'autre, dans le groupe comprenant un atome d'hydrogène, un radical alkyle en C_1 à C_8, alkyle ramifié en C_3 à C_8, cycloalkyle en C_3 à C_7, cycloalkylalkyle en C_4 à C_{10}, aralkyle en C_7 à C_{14}, 2-, 3- ou 4-pyridinyle, 2-thiényle, 2-furanyle, phényle éventuellement substitué par 1 à 3 groupes sélectionnés parmi: atomes de fluor, chlore, brome, groupe OH, radical alcoxy en C_1 à C_4, alkyle en C_1 à C_4, alkyle ramifié en C_3 à C_8, $CH_3S(O)_n$, NO_2, CF_3 ou NR^7R^8; ou

R^1 et R^2 peuvent former ensemble un groupe:



dans lequel:

L est O, $O(CH_2)_{m+1}O$, ou $(CH_2)_m$, m étant un nombre de 0 à 4;

R^3 est un atome d'hydrogène, un radical alkyle en C_1 à C_6, allyle, benzyle ou phényle éventuellement substitué par un atome de fluor, de chlore, un groupe CH_3, CH_3O ou CF_3;

R^4 est un radical alkyle linéaire en C_1 à C_8 éventuellement substitué par un atome de fluor; un radical alkyle ramifié en C_3 à C_8, cycloalkyle en C_3 à C_7, cycloalkylalkyle en C_4 à C_{10}, aralkyle en C_7 à C_{14}, dans lequel le radical aryle est éventuellement substitué par un à trois groupes choisis parmi les radicaux alcoxy ou alkyle en C_1 à C_4, les atomes de fluor, brome, chlore, les groupes NH_2, OH, CN, CO_2H, CF_3, NO_2, carboalcoxy en C_1 à C_4, NR^7R^8 ou $NCOR^7$; les radicaux alkynyle ou alkényle en C_3 à C_6, perfluoroalkyle en C_1 à C_3, phényle éventuellement substitué par un groupe choisi parmi les radicaux alcoxy ou alkyle en C_1 à C_4, les atomes de fluor, brome, chlore, les groupes NH_2, OH, CN, CO_2H, CF_3, NO_2, les radicaux carboalcoxy en C_1 à C_4, NR^7R^8 ou $NCOR^7$; les radicaux pentafluorophényle, benzyle éventuellement substitué par 1 à 3 groupes choisis parmi les radicaux alcoxy ou alkyle en C_1 à C_4, les atomes de fluor, brome, chlore, les groupes NH_2, OH, CN, CO_2H, CF_3, NO_2, carboalcoxy en C_1 à C_4, NR^7R^8 ou $NCOR^7$; les radicaux 2-, 3- ou 4-pyridinyle, pyrimidinyle ou biphényle;

R^5 est un atome d'hydrogène ou un radical alkyle en C_1 à C_6 ou benzyle;

R^6 est un atome d'hydrogène, un radical alkyle en C_1 à C_8, alkyle ramifié en C_3 à C_8, cycloalkyle en C_3 à C_7, alkynyle ou alkényle en C_3 à C_8, phényle éventuellement substitué par 1 à 3 groupes choisis parmi les radicaux alcoxy ou alkyle en C_1 à C_4, les atomes de fluor, brome, chlore, les groupes NH_2, OH, CN, CO_2H, CF_3, NO_2, carboalcoxy en C_1 à C_4, NR^7R^8 ou $NCOR^7$; les radicaux pentafluorophénylé, benzyle éventuellement substitué par 1 à 3 groupes choisi parmi les radicaux alcoxy ou alkyle en C_1 à C_4, les atomes de fluor, brome, chlore, les groupes NH_2, OH, CN, CO_2H, CF_3, NO_2, carboalcoxy en C_1 à C_4, NR^7R^8 ou $NCOR^7$;

R^7 et R^8 sont, indépendamment l'un de l'autre, choisis parmi l'atome d'hydrogène ou les radicaux alkyles en C_1 à C_4;

X est $S(O)_n$, O, NR^5, CH_2;

A est un radical alkyle en C_2 à C_{10}, alkyle ramifié en C_3 à C_{10}, alkényle en C_3 à C_{10}, ou alkynyle en C_3 à C_{10};

Y est O, S ou H_2;

Z est NHR^4, OR^4 ou R^4;

r est un nombre de 0 à 2,

et formant éventuellement un sel pharmaceutiquement acceptable en dérivant.

12. procédé selon la revendication **11**, comprenant en outre l'élimination de tout groupe protecteur sur R^3.

13. Un procédé selon la revendication **11**, comprenant en outre la réaction d'un composé de formule (I) dans laquelle Y est O, avec un réactif de Lawesson ou un pentasulfure diphosphoreux, pour conduire à un composé de formule (I) dans laquelle Y est S.

14. Un procédé selon la revendication **11**, comprenant en outre la réaction d'un composé de formule (I) dans laquelle Y est O, avec un agent réducteur tel que l'hydrure d'aluminium lithium ou du borohydrure de sodium, pour conduire à un composé de formule (I) dans laquelle Y est H_2.

15. Un procédé selon la revendication **11**, comprenant en outre la réaction d'un composé de formule (I) dans laquelle X est S, avec un agent d'oxydation convenable pour obtenir soit le sulfoxyde SO, dans lequel r est égal à 1, soit la sulfone SO_2, dans laquelle r est égal à 2.

16. Un procédé selon la revendication **11**, comprenant en outre la réaction d'un composé de formule (I) dans laquelle R^3 est un atome d'hydrogène, avec un agent d'alkylation convenable tel qu'un halogénure d'alkyle, pour conduire à l'obtention d'un composé de formule (I) dans laquelle R^3 est un radical alkyle en C_1 à C_6, allyle ou benzyle.

17. Un procédé de préparation d'une composition pharmaceutique consistant à mélanger une quantité efficace du point de vue thérapeutique d'un composé préparé selon l'une quelconque des revendications 1 à 16, et un support pharmaceutiquement acceptable.